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PYRIDINE AND ITS DERIVATIVES

In Four Parts

PART TWO

This is Part Two of the fourteenth volume published in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

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PYRIDINE
and Its Derivatives
Part Two

Erwin Klingsberg, *Editor*
American Cyanamid Company, Bound Brook, New Jersey

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds and accommodate the specific interests of the authors.

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ARNOLD WEISSBERGER

Preface

It is hoped that the organization of this monograph will prove to be self-explanatory, but a few general observations are in order.

Chemical compounds are tabulated exhaustively by the principle of latest position. Thus halogenated pyridinecarboxylic acids are found in Chapter X rather than VI, but hydroxy acids in Chapter XII. The principal exceptions are the quaternary compounds, which proved too numerous to be catalogued, and the N-oxides, which are included in Chapter IV irrespective of nuclear substitution. Other exceptions are explained where they occur.

The principle of latest position does not apply to reactions. All reactions for obtaining pyridine derivatives from non-pyridinoid starting materials are covered in Chapter II irrespective of substitution. If the starting material *is* a pyridine derivative, the reaction is discussed instead in the appropriate later chapter or chapters. Thus the conversion of aminopyridines to pyridinols is discussed in Chapters IX and XII.

Nomenclature follows Chemical Abstracts.

The editor wishes to express his gratitude to Prof. D. S. Tarbell of the University of Rochester for the impetus he gave to this undertaking, to the chemists in many parts of the world who have been so generous with reprints, to the staff of Interscience Publishers for their cooperation, and finally to Dr. R. S. Long and Dr. J. J. Leavitt of American Cyanamid for their patience.

Bound Brook Laboratories
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ERWIN KLINGSBERG

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CHAPTER III

Quaternary Pyridinium Compounds

By Elliott N. Shaw

Rockefeller Institute for Medical Research, New York *

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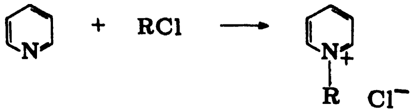
A. PREPARATION

1. Reaction of Organic Halides and Esters with Pyridines

The most general method of forming quaternary pyridinium compounds is by the action of an organic halide on a pyridine base, sometimes called the Menschutkin reaction (*1*). The transformation may be considered a displacement of the halogen as halide ion by the pyridine acting as a nucleophilic agent (III-1) (*3*). Rate studies indicate second-order kinetics generally (*1–3,5,10*). Evidence that the reaction is reversible is sometimes encountered (*10*). Polar solvents



(III-1)

generally favor the quaternization reaction (*4,6*) but increased rate is not always correlated with a higher dielectric constant (*439*). More important than the increased dielectric constant in the medium is the ability of solvents to solvate effectively the displaced halide ion (*237*).

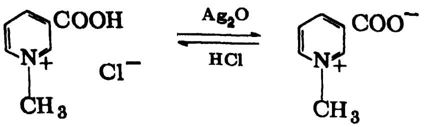
It follows that, so far as variations in the structure of R in the halide are concerned, their influence on the speed and course of the reaction is predictable from the familiar chemistry of halides in general towards nucleophilic agents such as hydroxide or ethoxide ions. Thus the reaction has preparative value in the aliphatic series when R is primary or, occasionally, secondary; among aromatic compounds, when groups activating the halogen are present (*viz.*, 2,4-dinitrochlorobenzene); and among heterocyclic compounds, when the halogen is reactive due to a particular orientation in the heterocycle (*viz.*, 4-chloropyridine). The reaction conditions of necessity vary widely. Methyl iodide combines with pyridine with the evolution of heat. A solvent may be used to temper the reaction. In many other cases, elevated temperatures are required to obtain a practical speed of quaternization.

a. Effect of Substituents in the Pyridine Ring

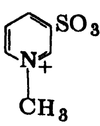
Substituents in the pyridine ring affect the ease of quaternization in the expected ways, to judge from various isolated observations which permit qualitative comparisons. Both steric and inductive influences are encountered. A systematic study of the properties of monoalkylpyridines by Brown and his colleagues (*8–11*) emphasizes steric inhibition by substituents in the 2 position. For example, Brown and Cahn (*10*) found a lowering of reaction rate with methyl iodide as the 2-alkyl group increases in size to *t*-butyl, for which the rate was about 1/4000 that of pyridine. The inductive effect of the substituent leads to a slight increase in basicity as measured with strong acids, but with bulkier Lewis acids, such as trimethylboron (*8*) or boron trifluoride (*11*), steric strain is manifest in the greater ease of dissociation of the complex or diminished heat of its formation (*11*) in contrast to the 3- and 4-isomer (*505–508*). 2,6-Di-*t*-butylpyridine fails to react with methyl iodide (*9*).

Failure to obtain quaternization with the reactive methyl iodide or dimethyl sulfate is rare. Even 2,6-dibromopyridine (*16*), 2,4,6-triarylpyridines (*434*), diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (*15*), and 3-nitro-*s*-collidine (*13*), bases in which one would expect steric and/or inductive effects to hinder the reaction, have been methylated. However, 2-chloro-5-nitropyridine (*90*), the 2- and 6-halonicotinamides (*30*) and 2-pyridinesulfonamide (*297*) reportedly do not react with methyl iodide. Halogens in the 2, 4, or 6 position of the pyridine ring undergo exchange with the halide of the alkyl halide (*44–46,53,84,85*) during quaternization (*cf.* p. 22).

When the pyridine base contains an acidic grouping such as carboxylic acid (*43,49*), sulfonic acid (*42*), or phenolic hydroxyl, the initial product of quaternization (*viz.*, III-2) may readily be converted to a form in which the positive charge on the nitrogen atom is internally compensated by ionization of the acidic group (III-3).



(III-2) (III-3)



Such quaternary derivatives are called betaines by analogy with the corresponding amino acid derivatives. Many variations have been encountered in which the negative charge may be borne, not only by oxygen, but also by nitrogen and carbon. Some of these will be considered later. Sometimes in quaternization of pyridinecarboxylic or -sulfonic acids, the betaines are obtained directly. They may be of such stability that it is not possible to convert them with acid to a quaternary halide form, as in the case of the betaine from 2-pyridinesulfonic acid (*297*), or the mono betaine derived from linking two molecules of nicotinic acid with an alkyl dihalide (*295*). Finally, it appears possible to crystallize bimolecular betaine salts in which a mole of carboxylate ion replaces an inorganic anion (*43, 296*).

The 2,2′-, 3,3′-, and 4,4′-bipyridyls have been converted to bis-quaternary salts (*430*).

b. Alkyl Halides and Related Alkylating Agents

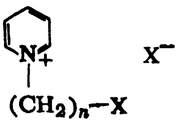
(a) Effect of Structure. Elimination as a Side Reaction. In the reaction of alkyl halides with pyridine bases, the rate decreases in the order I > Br > Cl. Alkyl esters may also be used as alkylating agents when the anion of a strong acid is formed, as in the case of sulfates, tosylates (*12,174*), or nitrates (*236*).

The ease of alkylation decreases as one proceeds from a primary halide or ester to a secondary or tertiary alkyl derivative (*10*). In the latter case, olefin formation predominates, a reaction that may also be encountered as a side reaction with primary or secondary halides. Noller and Dinsmore (*7*) concluded that a quaternary salt was not a necessary intermediate in the elimination reaction, although in some cases it may be (*41*). Olefin formation by this means has preparative value and has been widely used, particularly in steroid chemistry (*40*), for example, to convert a ketone to its α,β-unsaturated derivative via bromination and removal of hydrogen bromide. The use of collidine (*39*) is apparently advantageous since it is not only a stronger base than pyridine but sterically less disposed towards quaternization reactions.

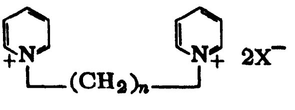
When quaternization takes place at an asymmetric carbon atom, optical activity may be retained (*26*), probably with inversion.

In recent years, 1-alkylpyridinium salts have been prepared in great numbers, particularly from halides containing twelve to eighteen carbon atoms (*17,50–52*). Such quaternary salts have germicidal properties (*442*), which do not appear to be specific for pyridinium compounds but, instead, related to the surface activity generally encountered in solutions of ammonium ions with long chain hydrophobic groups.

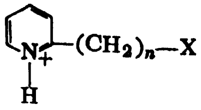
The methylene dihalides, $X(CH_2)_nX$, react readily with pyridine, forming bis-quaternary salts of the type (III-5) where $n = 1$ (*21*), 2 (*22*), or 2, 3, 4, 5, and 10 (*23,25*). The picolines (*23*) and nicotinic acid and amide (*29*) react similarly. 2,4-Dibromohexane also provides bis-quaternary salts (*23*). It has been possible, with equimolar amounts of pyridine and trimethylene dihalides, to obtain mono quaternary derivatives (III-4, $n = 3$) in good yield (*24*). Pyridylalkyl halides such as III-6 are stable as salts, but it is apparent that inter- or intramolecular condensation would be encountered under certain conditions.



(III-4)

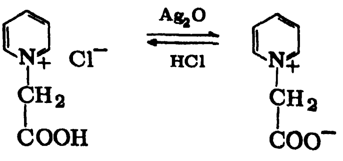


(III-5)



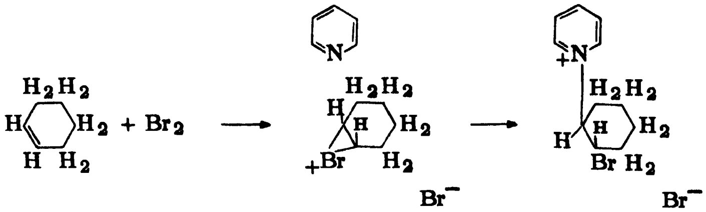
(III-6)

Alkyl halides containing other functional groups may undergo quaternary salt formation. Thus styrene halohydrins (*47,53,57*) and propylene halohydrins (*24,54,56*) yield pyridinium salts without difficulty (such as oxide formation). Mono- and dibromo (*28*) ketones may form mono- and diquaternary salts, although hydrogen bromide elimination may occur as a side reaction (*31,40*). Equimolar amounts of chloroacetic acid and pyridine yield a quaternary salt (III-7) (*18*) in contrast to the action of the stronger acid, trichloroacetic, which forms a carboxylate salt by transfer of a proton (*19*). Such a product is at once distinguishable from a quaternary salt since the addition of alkali liberates pyridine. Treatment of the quaternary chloride with base permits the isolation of pyridine betaine (III-8). This behavior is characteristic of halo acids. With β-bromo acids, some elimination may be encountered (*60*).



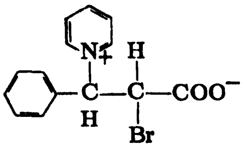
(III-7) (III-8)

(**b**) **Quaternization by Halogenation in Pyridine.** A number of cases are reported in which halogenation (by addition or substitution) and pyridinium salt formation have been achieved in a single operation. In the reaction of cyclohexene and bromine in pyridine to form 1-(2-bromocyclohexyl)pyridinium bromide, the mechanism does not appear to be stepwise (*33,34*); the cyclohexene dihalide does not react readily with pyridine under the conditions of the reaction. The product is considered to be trans and a mechanism has been proposed (III-9) (*34*).



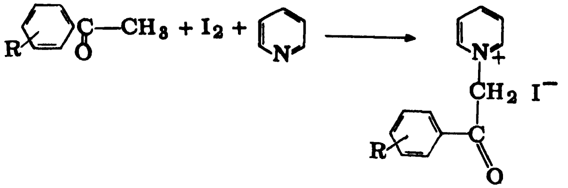
(III-9)

Cinnamic acid, when brominated in pyridine, leads to the betaine III-10. With ethyl cinnamate, the corresponding quaternary ester, which initially forms, undergoes a ready β-elimination of pyridine on treatment with dilute ammonium hydroxide, providing good yields of ethyl α-bromocinnamate (*33*).



(III-10)

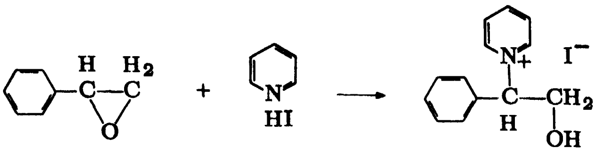
Iodination of ketones in pyridine has been shown by King (*35–37*) to be a useful route to 1-phenacylpyridinium iodides (III-11).



(III-11)

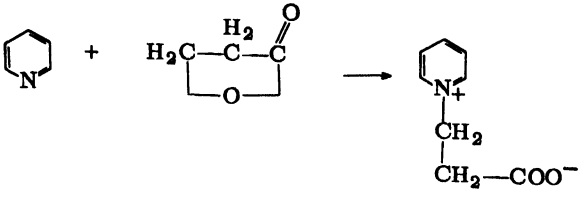
Since such quaternary compounds cleave readily with alkali to a benzoic acid (*48*), a convenient degradation of a methyl ketone to the lower carboxylic acid is provided, exemplified by the synthesis of hydroxybenzoic acids (*36*). (*Cf.* p. 45.) In the halogenation, the pyridine promotes enolization of the ketone in the rate-determining step (*367*). 2-Picolinium salts have been considered to show methyl activation similar to methyl ketones and, in fact, undergo iodination in pyridine (*401*). Active methyl groups in other heterocycles have also been iodinated in pyridine with formation of a pyridinium iodide (*470,499*).

(c) Alkylation by Oxides, Lactones, and Sultones. Pyridine hydroiodide combines quite readily with styrene oxide to form mainly that quaternary salt bearing the primary alcoholic group (III-12) plus a small amount of the isomeric secondary alcohol (*55*). The structures were proven by alternate syntheses. Halohydrins do not appear to be intermediates, since they react more slowly than styrene oxide (*55*). Reaction with cyclohexene oxide led to a 1-(*trans*-2-hydroxycyclohexyl)pyridinium salt (*503*).



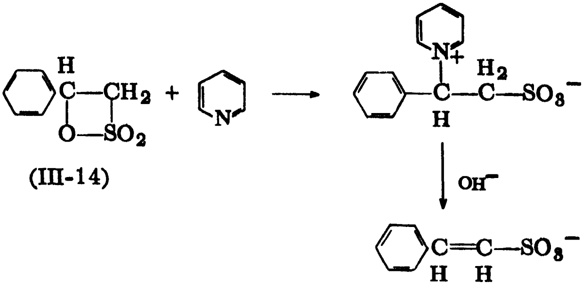
(III-12)

Propiolactone in ether solution undergoes ring opening with pyridine, the betaine (III-13) precipitating at once (*59*). With 2-aminopyridine the reaction follows the same course; however, 2-amino-5-bromopyridine is alkylated on the amino group and not at the ring nitrogen (*107*).



(III-13)

Somewhat similar to the above reactions is the formation of a sulfonic acid betaine (III-15) on treatment of the styrene–sulfur trioxide adduct (III-14) with pyridine (*144*). The elimination of pyridine from betaines of this type under alkaline conditions (*144, 145*) is analogous to the behavior of certain carboxylic acid pyridinium betaines (*cf.* p. 16).

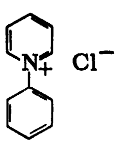


(III-14)

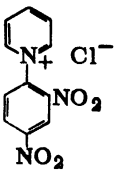
(III-15)

c. *Aryl Halides*

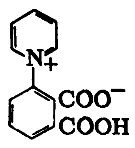
(a) Displacement of Activated Substituents from the Aromatic Ring by Pyridine. Aryl quaternary pyridinium derivatives such as 1-phenylpyridinium chloride (III-16) are known but usually must be obtained by indirect methods (see p. 58), although pyridine can be phenylated by using diphenyliodonium fluoroborate (*495*). Aryl halides, however, react readily only when activated by nuclear substituents such as nitro or carboxyl. Thus, 2,4-dinitrochlorobenzene forms a crystalline pyridinium salt (III-17) with ease. The chemistry of this substance as explored by Zincke (*61,62*) is of particular interest in the opening and re-closing of the pyridine ring, described later (p. 58). Not all derivatives of pyridine react with 2,4-dinitrochlorobenzene. In particular, difficulty has been encountered with 2- and 4-alkyl-substituted pyridines (*67,68*), whereas the 3-isomers generally give crystalline salts. A variety of other substituents in the 3 position (except chloro, bromo, nitro, and carbethoxy groups) permit quaternization (*264*). With 4-acetylamino- or 4-anilinopyridine no difficulty was encountered (*264*), but with 4-alkoxy or 4-alkylthio substituents the quaternization was complicated by an elimination reaction leading to 1-(2,4-dinitrophenyl)-



(III-16)



(III-17)

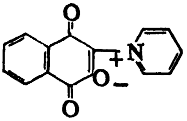


(III-18)

4(1*H*)-pyridone (*265*) in addition to the usual product. Since the quaternary salt (III-17) readily splits to dinitrophenol and pyridine on treatment with nitrite (*62*), β-picoline derivatives can be purified through intermediate formation of a dinitrophenyl quaternary salt (*67*).

Chlorine atoms have also been displaced by pyridine in 2-chloro-3,5-dinitrobenzoic acid (*66*), 1,3-dichloro-3,5-dinitrobenzene (*64*), and 3,6-dichlorophthalic anhydride (*69*). The dichloro compounds give bis-quaternary salts. When a carboxyl group is present, the betaine is isolated readily. A nitro group may be displaced, presumably as nitrite ion, from *o*-dinitrobenzene (not *p*-isomer), 2,3-dinitrobenzoic acid, and 3-nitrophthalic anhydride (*69*). Isolation of a pyridinium salt in such cases was possible only where carboxyl groups permitted stabilization through betaine formation as in III-18, formed from 3-nitrophthalic anhydride. In contrast to these nitro compounds reactive to pyridine, Balfe, Doughty, and Kenyon observed that a number of closely related compounds (*69*) were inert to pyridine. Similar to these aromatic quaternizations is the condensation of 2,4,6-trinitroanisole with pyridine (*65*). Here, however, the pyridine attacks the methyl group, displacing the picrate ion to form 1-methylpyridinium picrate. Displacements by pyridine in aromatic systems have been studied kinetically (*78,457*).

(b) Haloquinones. Enol Betaines. Chemists investigating the chemistry of quinones in pyridine as a solvent often have encountered a reaction of pyridine with the quinone. In the case of chloroquinones, there are three ways in which this may happen. One is the addition of pyridine to the unsaturated system, a type of reaction treated later (p. 19). Here it should be noted that the halogen in haloquinones is readily displaced by pyridine as it is by other agents. Thus, 2,3-dichloro-1,4-naphthoquinone combines with pyridine, losing a second chlorine by solvolysis, to form the yellow enol betaine (III-19) (*110*). A similar reaction is pictured as taking

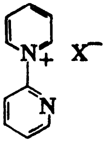


(III-19)

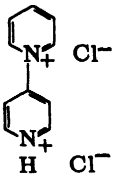
place with chloranil, with formation of a mono- or dibetaine (*111*). Enol betaines are formed from a variety of α-chloro ketones, both acyclic (*38*) and cyclic (*113*), and are discussed more fully elsewhere (p. 43).

Pyridine bases also form addition compounds with quinones which are of the molecular complex type, as opposed to the quaternary compounds formed by addition of pyridine to unsaturated systems. While pyridine and 4-picoline form water-soluble quaternary chlorides with chloranil, 2-picoline and other bases form 1:1 complexes under the same conditions, *i.e.*, in anhydrous benzene or chloroform (*150*). From the molecular adducts the components are readily recovered by very mild methods, including treatment with certain organic solvents.

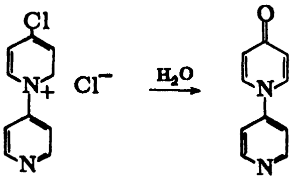
d. Pyridylpyridinium Salts



(III-20)



(III-21)



(III-22)

Since the halogen atoms in the 2 and 4 positions of the pyridine nucleus have notable reactivity, their displacement by tertiary amines with formation of quaternary salts is not unexpected. In the case of 4-chloro- and 4-bromopyridine (*74,75*) and even of 4-nitropyridine (*76*), the reactivity of the substituent leads to self-condensation at room temperature, a reaction which limits the stability of these bases. The behavior of 4-chloropyridine is typical of this. Stored samples were observed to have increased solubility in water and ionic halogen content (*74*). Characterization of a 1-(4-pyridyl)-4-chloropyridinium chloride was not achieved, perhaps because of the presence of further condensation products in the mixture, but from aqueous solutions of the product the known 1-(4-pyridyl)-4(1*H*)-pyridone (III-22) was readily isolated. In the case of 2-pyridyl halides this auto-condensation does not appear to be a difficulty, but quaternization reactions leading to pyridylpyridinium salts have been reported. Even before the isolation of such ions, their formation was suspected, as in the conversion of 2-chloropyridine to 2-aminopyridine when heated by itself at 200° (*82*). 2-Iodopyridine has been condensed with pyridine (*73*). A kinetic study of the reaction of 3-nitro-2-chloro- and 5-nitro-2-chloropyridine with pyridine indicated that the reaction is second order, showing similarity to the aliphatic S_N2 mechanism; the quaternary compounds formed were characterized (*78*).

The most important pyridylpyridinium compound is 1-(4-pyridyl)pyridinium chloride hydrochloride (III-21), introduced by Koenigs and Greiner (*71*). This substance, m.p. 158–160° (*83*), is formed by the action of thionyl chloride on pyridine at room temperature (*71,83,109*), presumably by way of 4-chloropyridine which then forms a salt with unchlorinated pyridine. Before the potentialities of pyridine 1-oxide were realized (*cf.* Chapter IV), this quaternary compound was the main route to certain 4-substituted pyridines, since its hydrolysis provides 4-pyridinol (*71,83,109*) and its ammonolysis, 4-aminopyridine (*71,81,276*). Through reactions with sodium alcoholates and mercaptans, 4-pyridyl ethers (*71,79*) and thioethers (*518*) are formed. In the reaction with amines to form 4-arylaminopyridines, best yields were obtained under conditions that minimized ring opening of the pyridylpyridinium salt to other products (*519*). Among the improved syntheses of 1-(4-pyridyl)pyridinium halides (*cf.* review *517*), the aluminum chloride–catalyzed bromination of pyridine in a solvent at room temperature is of both practical and theoretical interest (77). Attempts to extend the preparation of a 1-(4-pyridyl)pyridinium salt to other pyridine bases succeeded with 3-picoline (*212*) but not with 2-picoline and its 5-ethyl derivative (*517*).

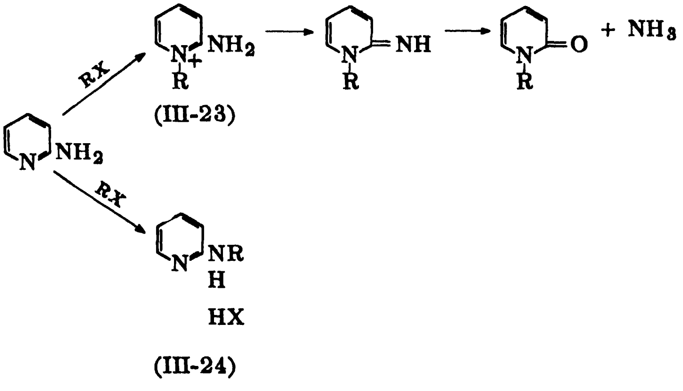
The oxidation of pyridine itself by potassium persulfate leads to a 24% yield of 1-(2-pyridyl)pyridinium salts (III-20). The structure proof is based on degradation to 2-aminopyridine and glutaconaldehyde (*70*). Later oxidation studies revealed the simultaneous formation of a small amount of the 3-pyridyl isomer (*72*).

In other heterocyclic series, active halogens are, of course, also found, and their quaternization reactions have been studied, *viz.*, pyrimidines (*431*) and triazines (*437*). 5,5-Dihalobarbituric acids give halogen-free betaines with pyridine and 4-picoline, but not with 2-picoline (*158*).

e. Selective Quaternization

As shown earlier, substituents in the pyridine ring affect the reactivity of the base towards combination with alkyl halides at the 1 position. When the substituents are themselves capable of being alkylated, the site of reaction is also in question. Limited observations have been made on the course of the reaction with pyridines containing amino, thio, and other substituents. A quaternary pyridinium compound bearing such groups can often best be prepared by introducing the substituent after quaternization.

The reaction of aminopyridines with alkyl halides was studied by Chichibabin and his co-workers. 2-Aminopyridine alkylates predominantly at the ring nitrogen atom with methyl or benzyl halides, yielding a 1-alkyl-2-aminopyridinium halide (III-23) plus small amounts of the isomeric 2-alkylaminopyridine (III-24) (*87*). (Side chain alkylation occurs exclusively when the sodium salt of 2-aminopyridine is used instead of the free base (*87,91,94*).) Alkylation at the 1 position appears to be rather general and has been reported to occur with long chain alkyl halides (C_{10}–C_{14}) (*94*), certain polymethylene dihalides (C_6–C_{10}) (*93*), diethylaminoethyl chloride (*96*), chloroacetic acid (*102–104*), 2,4-dinitrochlorobenzene (*105*), and α-chloroketones (*98*). 4-Aminopyridine similarly alkylates on the ring (*88*).

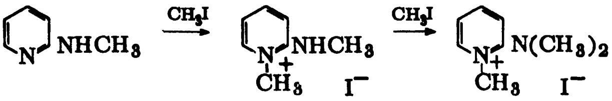


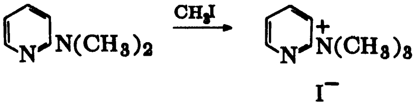
(III-23)

(III-24)

Evidence for the course of reaction was provided by treatment with alkali. Thus Chichibabin showed that the methylation product (III-23, R = CH_3) yielded ammonia and 1-methyl-2(1*H*)-pyridone (*87*).

Like 2-aminopyridine, 2-methylaminopyridine forms a 1-methyl quaternary iodide (III-25) on reaction with methyl iodide. However, 2-dimethylaminopyridine quaternizes at the side-chain nitrogen atom (III-26) (*89*). Perhaps in this case the basicity of the substituent amino group has been significantly increased. The isomeric product (III-27) was synthesized for contrast. Side-chain alkylation also occurred in the methylation of 3- or 5-nitro-2-aminopyridine (*90*).


(III-25) (III-27)


(III-26)

Among sulfur-containing pyridines, a thiol (or thione) grouping alkylates in preference to quaternization at the ring nitrogen under the usual conditions (*86*). However, the methylthio group forms a sulfonium salt less readily. Thus, 2-methylthiopyridine yields the quaternary methiodide (III-28) (*99*) or ethiodide without difficulty.

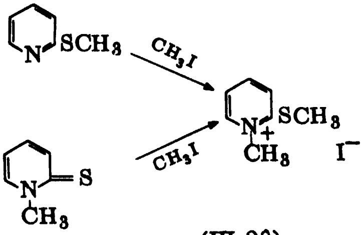

(III-28)

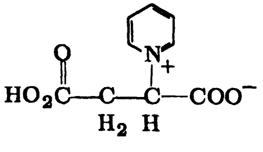
TABLE III-1. Some Quaternary Pyridinium Salts

Base	1-Substituent	Anion	m.p., °C.	Ref.
Pyridine	methyl	I^-	117	275
			123–25	293
		tosylate	138–39	12
	ethyl	I^-	90.5	181
	n-propyl	I^-	52–53	487
	i-propyl	I^-	114–15	487
	benzyl	Cl^-	105–106	61
	2,4-dinitrophenyl	Cl^-	190–210	61
	phenacyl	Br^-	198	488
	4-pyridyl	Cl^-	158–60	83
2-Picoline	methyl	Br^-	217	489
		I^-	224	489
		tosylate	149–50	12
	ethyl	I^-	123	489
	n-propyl	I^-	77	489
	i-propyl	I^-	142	489
	n-butyl	I^-	98	489
	benzyl	Cl^-	99	492
	phenacyl	Br^-	215	384
3-Picoline	methyl	I^-	79–80	44
	benzyl	Cl^-	220	492
4-Picoline	methyl	I^-	157–58	293
	benzyl	Cl^-	78	492
2,4-Lutidine	benzyl	Cl^-	212	492
2,6-Lutidine	benzyl	I^-	121	14
2,4,6-Collidine	methyl	ClO_4^-	201–202	14
	benzyl	I^-	102	14
	SUBSTITUTED PYRIDINES			
2-Bromopyridine	ethyl	Br^-	194–95	44
3-Bromopyridine	methyl	I^-	159–60	44
2-Chloropyridine	methyl	tosylate	149–50	
2-Iodopyridine	methyl	I^-	209.5–10	44
Methyl nicotinate	methyl	I^-	129.5–30	44
Nicotinamide	methyl	I^-	204	316
Nicotinonitrile	methyl	I^-	194.5–96	44

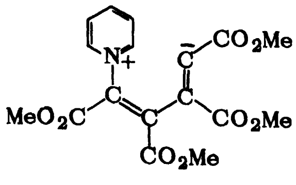
A similar example was reported earlier with 4-methylthio-2,6-lutidine (*243*). In these cases, the structures of the products were proved by synthesis from *N*-alkylthiopyridones as shown. In other heterocyclic series an interchange of *N*- and *S*-alkyl groups may occur, yielding, when the alkyls are different, a mixture of four quaternary compounds. Apparently intermediate sulfonium salts are involved (*99*). Although such a complication was not encountered in quaternization of the simple alkylthiopyridines studied, its possible appearance in other cases remains. For preparation of quaternary derivatives of alkylthiopyridines, therefore. it is preferable to start with 1-alkyl-2-thiopyridones since the latter readily alkylate on the sulfur atom unambiguously (*92,99,100*). A few observations have shown alkylation of ring nitrogen in the presence of trivalent phosphorus and arsenic substituents (*97*).

2. By Addition of Pyridines to Unsaturated Systems

In many instances, pyridine has been found to add across double bonds activated by carbonyl or similar groups. Since pyridine often is chosen solely for its superior solvent properties, or weak basicity, these reactions were occasionally an unexpected complication. Lutz observed (*26*) that the salt of pyridine and maleic acid, m.p. 105°, when held a few minutes at its m.p., was converted to the betaine, m.p. 191° (III-29, the ionized carboxyl arbitrarily selected). The same product formed slowly in solution at room temperature. The structure is confirmed by the more conventional preparation from bromosuccinic acid. The addition took place to fumaric acid as well and with alkyl derivatives of pyridine (*119*). Using potentiometric titration and interpreting loss of acidity as evidence of addition, Lutz, Klein, and Jirgenson (*119*) found that itaconic, crotonic,



(III-29)

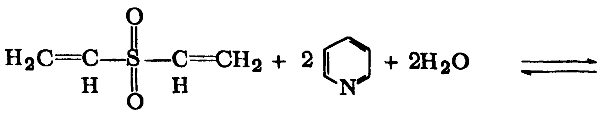


(III-30)

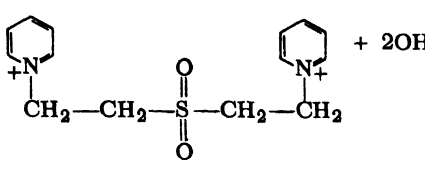
and aconitic acids added pyridine, whereas citraconic, mesaconic, allylmalonic, and cinnamic acids did not under the same conditions.

Pyridine has been investigated as a dienophile in the Diels-Alder reaction (*136–141*). With dimethyl acetylenedicarboxylate in ether, a red, labile quaternary intermediate forms from two moles of ester per mole of base, which Diels and co-workers choose to represent as the carbanion betaine (III-30). Stable bicyclic products are also formed. This work has been reviewed by Norton (*142*).

When pyridine adds to one carbon atom of a double bond, a proton is apparently picked up by the adjacent carbon to saturate the olefinic linkage. The participation of water in this way is clearly shown in the addition of pyridine to vinyl sulfone (III-31) in aqueous solution (*129*). The reaction is reversible and leads to the formation of a bispyridinium salt (III-32) with an increase in pH. The crystalline dichloride of III-32 can be isolated; a freshly prepared aqueous solution of it rapidly becomes acidic to an extent indicating formation of an equilibrium mixture of pyridine hydrochloride and vinyl sulfone. Vinyl sulfoxide behaves similarly, but more slowly.

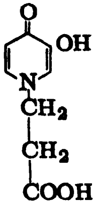


(III-31)

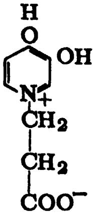


(III-32)

Some features of the chemistry of leucenol (mimosine) appear pertinent to the discussion. The pyridone structure (III-33) was arrived at through the efforts of Adams (*127,128,132*), Wibaut (*125,126*), Bickel (*131*) and co-workers; this work is discussed in Chapter XII. The betaine structure (III-34) was also considered

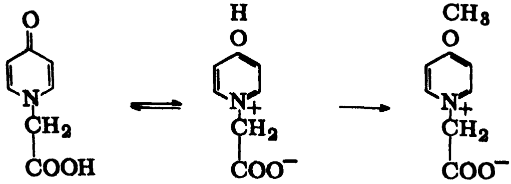


(III-33)



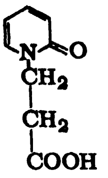
(III-34)

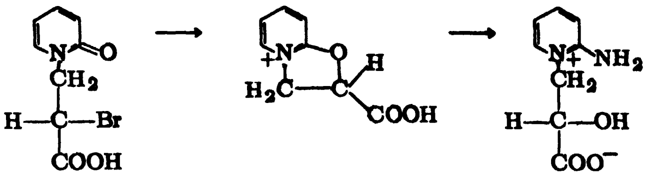
(*126*), and although the pyridone structure is favored by spectroscopic considerations, the tautomerism may advantageously be kept in mind in considering the transformations of such systems. Thus, 4-oxo-1(4*H*)-pyridineacetic acid on methylation forms the 4-methoxypyridine quaternary salt (III-36) (*108*). In the degradative studies of leucenol (III-33), β-elimination reactions were encountered reminiscent of the reversible addition-elimination chemistry of pyridine and active unsaturated systems. For example, the action of heat or of dimethyl sulfate in alkali leads to the formation of 3,4-pyridinediol or its 3-methyl ether plus, presumably, an acrylic acid fragment.



(III-35) (III-36)

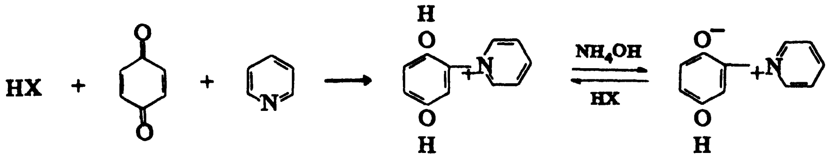
Like the pyridine bases, 2(1*H*)-pyridone adds to acrylic acid derivatives (*130,132–134*). Reversibility is indicated since 2(1*H*)-pyridone is eliminated by the action of heat or strong alkali on the acid (III-37) obtainable from acrylonitrile and 2(1*H*)-pyridone followed by hydrolysis (*132*). Very often the initial adduct of a pyridone or aminopyridine to an unsaturated compound cannot be isolated because of subsequent changes, such as ring closure. Thus, from the addition of 2(1*H*)-pyridone to α-bromoacrylic acid, the cyclized product (III-38) was obtained (*134*) which opened with ammonia to yield a betaine (III-39). The latter also resulted from the addition of 2-aminopyridine to acrylic acid (*147*); with ethyl acryl-


(III-37)



ate, cyclization occurred. Adams and Pachter (*147*) point out that the addition reactions of 2-aminopyridine may be influenced by other substituents that favor addition of the amino nitrogen rather than the ring nitrogen and that the nature of the product must be deduced from additional evidence. Spectroscopy is very helpful in such situations (*134*). (*Cf.* p. 78.)

During studies on the halogenation of hydroquinone in pyridine, Ortoleva (*115*) isolated a compound later shown to be a (dihydroxyphenyl)pyridinium salt (III-40) by Barnett, Cook, and Driscoll (*120*). The original work demonstrated that pyridine added to benzoquinone under acid catalysis. Organic (*120*) as well as inorganic acids facilitate the reaction, which proceeds readily with pyridine or 2-picoline even in chloroform at room temperature (*122*),



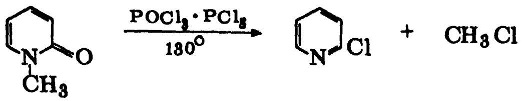
(III-40) (III-41)

the salt crystallizing out. The betaine (III-41) can be precipitated from aqueous solutions of the quaternary salts on treatment with ammonia or carbonates (*120,123*). Other aromatic quinones may participate in this reaction (*120,121,146*). Some pyridine-catalyzed polymerization processes of quinones are thought to proceed through pyridinium adducts which may be active intermediates (*123,124*). The *p*-quinone imide, 1,4-naphthoquinonedibenzenesulfonimide, also adds pyridine in dilute acid to form a quaternary salt in a manner analogous to *p*-quinones (*135*).

Since many of the addition reactions of pyridines to quinones lead to more complex ring systems, further details are found in a later section (p. 79).

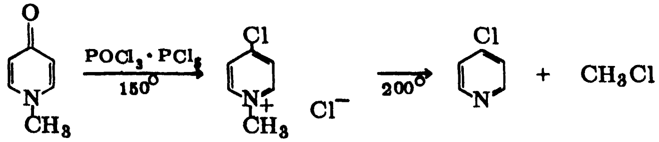
3. From Pyridones and Thiopyridones

Conversion of pyridones to halopyridines by means of phosphorus halides is a familiar transformation in pyridine chemistry. When the pyridone bears a 1-substituent, this may or may not be lost in the reaction. Thus 1-methyl-2(1*H*)-pyridone was demethylated (*114*),



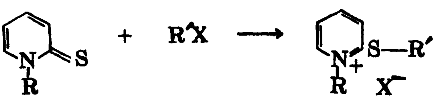
(III-42)

yielding 2-chloropyridine (III-42), whereas the 4-isomer (III-43) readily gave 1-methyl-4-chloropyridinium chloride (*45*), dealkylation being observed only above 200°. Among the 1-alkyl-2-pyridones dealkylation is not generally obligatory; certain structures or milder conditions will permit the isolation of 1-alkyl-2-chloropyridinium salts. Thus a number of 1-phenethyl-2-pyridone derivatives, when heated with phosphorus oxychloride in xylene, gave the expected 2-chloro quaternary salts (*172,401*).



(III-43)

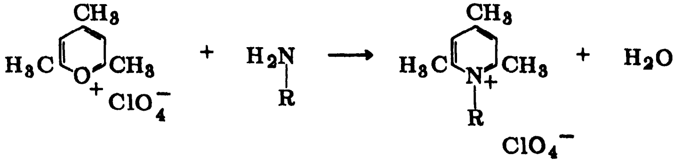
1-Phenyl-4(1*H*)-pyridone has been converted to 1-phenyl-4-chloropyridinium chloride by the action of thionyl chloride (*170*). 1-Alkyl-2(or 4)-thiopyridones alkylate readily on the sulfur atom (III-44) (*92,100*). This method of preparing pyridinium salts bearing an alkylthio group is less ambiguous than the quaternization of alkylthiopyridines, in which group exchange may occur (p. 22).



(III-44)

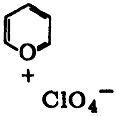
4. From Pyrylium Salts

Pyrylium salts react smoothly with primary amines even at room temperature to yield pyridinium salts (*161*). The usefulness of this reaction is limited by the lack of flexibility in synthesis of the starting materials. However, the yields are good. Either alipathic or aromatic primary amines may be used with 2,4,6-trimethylpyrylium perchlorate (III-45). 2,4,6-Triarylpyrylium perchlorates behave similarly towards methylamine (*161*) or aniline and its derivatives (*162–165,167*). It is of interest that secondary amines and 2-methylpyrylium salts give a benzenoid amine by entrance of the methyl group into the ring (*173*).

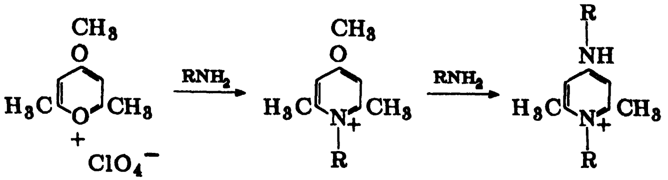


(III-45)

The parent member of the pyrylium salts (III-46) has only recently been prepared (*169*) by cyclization of glutacondialdehyde obtained by a ring opening reaction of pyridine. The pyridine ring was harder to form from pyrylium itself than from its substituted derivatives (*169*). Although a methoxyl group in the 4 position (III-47) can be displaced by amines and thiols (*166,168*), replacement of the ring oxygen is more rapid. Thus it was possible, with primary amines, to obtain a stepwise reaction leading first to the 4-methoxylutidinium ion (III-48) and then, with replacement of methoxyl, to the aminolutidinium salt (III-49). With secondary amines, 4-dialkylaminopyrylium salts were formed (*166,168*). A methylthio group was similarly replaceable by amines (*168*).



(III-46)



(III-47) (III-48) (III-49)

Conversion of distyrylpyrylium to distyrylpyridinium salts has been reported (*171*).

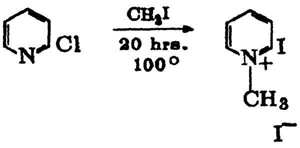
This reaction is also discussed in Chapter II; see p. 210 and Table II-29 (pp. 217 ff.).

5. By Transformation of Other Pyridinium Salts

In this section many of the unique chemical properties of pyridinium salts are illustrated, anticipating the fuller discussion of their reactions later. However, to emphasize the usefulness of these reactions as synthetic methods for quaternary compounds, it seems profitable to consider certain properties of pyridinium salts here. Faced with the problem of preparing any of the quaternary salts whose synthesis is mentioned below, one may, of course, consider carrying out transformations on tertiary bases leaving the quaternization reaction until the end. In some instances such a route would be much more difficult.

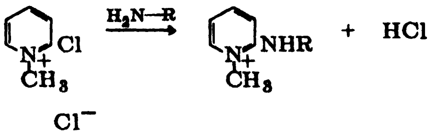
a. Displacement of Ring Substituents in Pyridinium Compounds

During quaternization of 2-chloropyridine with methyl iodide at 100°, the ring chloro group was replaced by iodo with formation of 1-methyl-2-iodopyridinium iodide (III-50) (*45*). A similar exchange was encountered in the reaction at 120° of 4-chloro-2,6-lutidine with ethyl iodide (*243*). The exchange reaction appears to occur after the quaternization and to indicate a greater reactivity towards displacement of the ring halogens in the pyridinium compounds. Even near 50° 2-chloro- and 2-bromopyridine give some 2-iodopyridine methiodide. 2-Fluoro- and 3-bromopyridine at 90° undergo quaternization without exchange. The replacement of the ring bromine in 1-ethyl-2-bromopyridinium bromide by iodide ion was demonstrated (*44*). On the other hand, 2-iodopyridine and benzyl bromide gave the normal product (*246*).



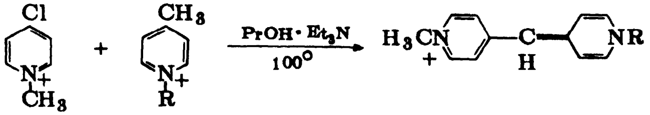
(III-50)

The reactivity of groups in the pyridinium salts has been of value in synthesis. Thus a 2-chloro (*45,245*) or 4-chloro (*46,244*) atom is readily replaced by ammonia and amines in alcoholic solution (III-51). Alkoxy or thio groups are likewise displaced by amines under similar reaction conditions (*166,168,247*).

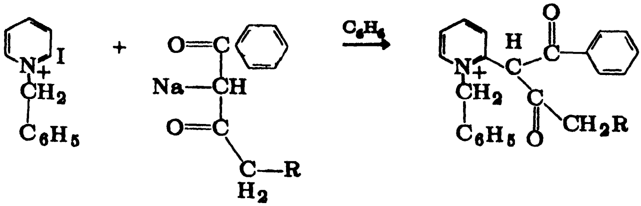


(III-51)

Pyridylation of a carbon atom by a halopyridinium salt is an interesting example of the usefulness of increased reactivity of substituents in the quaternary salt. Types described include the pyridylation of the methyl group in a 4-picolinium salt, which afforded the cyanine dye (III-52) (*189*), and the pyridylation of the methylene group in a 1,3-diketone (III-53) (*246*). The latter condensation also succeeded with a 3-methoxy group in the pyridine ring. The anhydro bases were isolated (*246*). Acetylacetone could not be arylated.



(III-52)

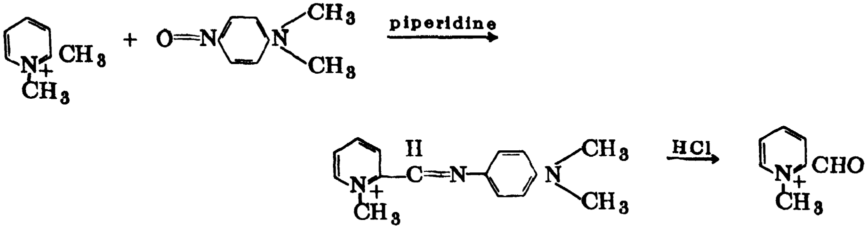


(III-53)

R = 3-(4-quinazolonyl-)

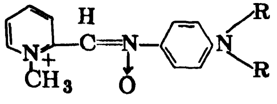
b. Condensation Reactions Leading to Pyridinium Alcohols and Olefins. Cyanines

(a) Adjacent to a Ring Carbon. The methyl groups in 2- and 4-picoline are notably reactive to certain reagents. In their quaternary salts the reactivity is heightened, and condensations become possible on the methyl group that are either more difficult or impossible with the bases themselves (*cf.* pp. 36 ff.). Thus 2-picoline methiodide undergoes a piperdine-catalyzed condensation with *p*-nitrosodimethylaniline in ethanol solution. Initially, the anil (III-54) was identified as the product by its easy hydrolysis to the aldehyde (III-55) isolated in good yield as the phenylhydrazone (*197*). Subsequently it was shown that a nitrone (III-54a) could be isolated from similar reactions (*479*) and that the relative amounts of these products depended markedly on reaction conditions (*468*). Combination with *p*-nitrophenylnitrosamine was also reported (*200*). In these cases the parent bases failed to react. 2-Picoline methiodide did not combine with a benzene diazonium salt (*480*). (*Cf.* p. 493.)



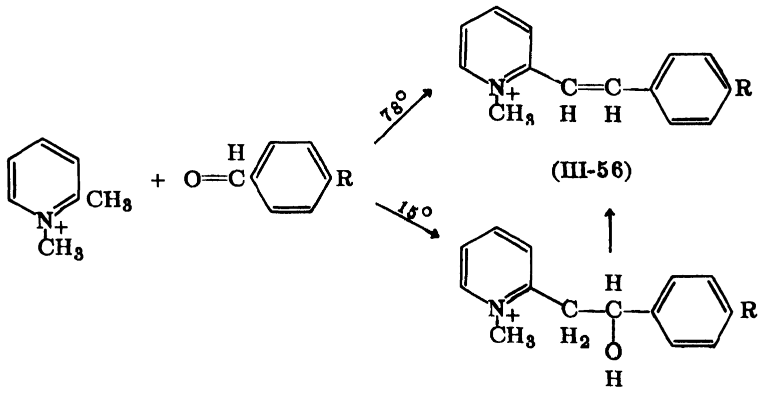
(III-54)

(III-55)



(III-54a)

The condensation of the picoline quaternary salts with aldehydes has been widely studied. As generally carried out, by refluxing the aldehyde and quaternary picolinium salt in ethanol containing piperidine (*198,205*), the reaction proceeds to the stilbazole quaternary salt (III-56) in good yields. Aromatic aldehydes have been used chiefly. These may be in the form of Schiff bases (*219*). 2-Picoline methiodide (*198,204,205*) and 4-picoline methiodide (*209, 207*) condense about equally well. However, reports (*215*) that 3-picoline methiodide formed a stilbazole were not supported by a careful study with purified 3-picoline (*208*). In the case of 2-ethyl- and 2-phenethylpyridine methiodides, the reaction did not take place under the usual conditions; steric hindrance was considered responsible for the failure (*206*). With the reactive carbonyl compound, isatin, the condensation with 2-picoline was more readily controlled than with the corresponding methiodide (*218*). In general, of course, quaternary derivatives of the stilbazole type (III-56) are obtainable by the reaction of alkyl halides with stilbazoles (*213*).

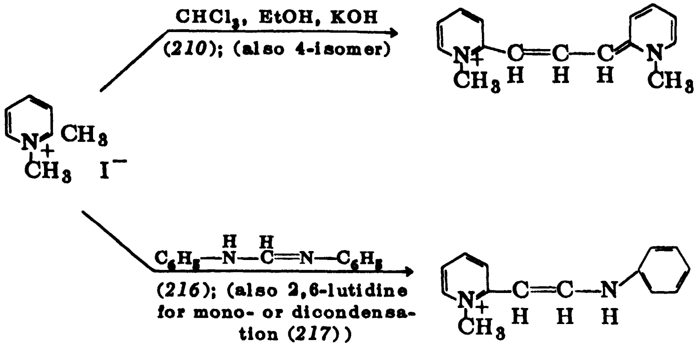


(III-56)

(III-57)

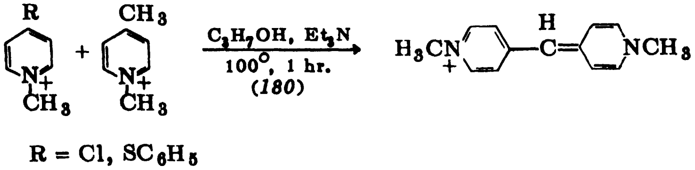
By carrying out the ethanolic condensation of 2-picoline methiodide and benzaldehyde at 15°, it has been possible (*238*) to obtain an intermediate carbinol (III-57) which readily dehydrates under the ordinary conditions of reaction. Carbinols were also obtained from a number of nitro- and halogen-substituted benzaldehydes, but in other cases the reaction could not be stopped at this intermediate stage (*214*).

Recognition of the photosensitizing properties of III-56 (R = $(H_3C)_2N$) (*198*), as well as the relationship of this substance to cyanines in general, stimulated much further work. The subject has been reviewed (*211*) and the relationship between structure and color has been interpreted (*220,277,429*). Some variations in the condensation reactions of picoline quaternary salts have appeared in the development of the cyanine dyes and are noted for their chemical interest (III-58–III-60). In 2,4- and 2,6-dimethylpyridine methiodides, both methyl groups react (*209,171*).


CHCl3, EtOH, KOH
(210); (also 4-isomer)
CH3
I⁻
C6H5—N—C=N—C6H5
(216); (also 2,6-lutidine for mono- or dicondensation (217))

(III-58)

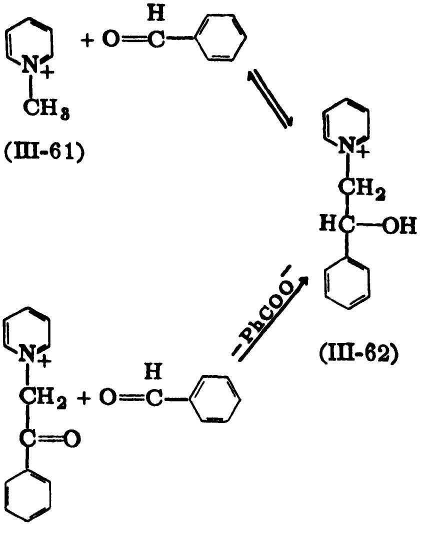
(III-59)



(III-60)

Side chain reactivity is also revealed in the easy dehydrogenation of the bismethiodide of 1,2-bis(4-pyridyl)ethane to the ethylene (*293*).

(b) Adjacent to the Ring Nitrogen. In addition to the well-known condensation of aldehydes with 2- and 4-alkyl side chains in pyridinium compounds, a methylene group at the ring nitrogen atom shows similar behavior. This type of reaction has been studied chiefly by Kröhnke and his collaborators (*48*, a review). For example, 1-methylpyridinium salts (III-61) combine with benzaldehyde in alcohol containing piperidine to form 1-(β-hydroxyphenethyl)-pyridinium salts (III-62) (*232*). The reaction appears to be much slower than that of the 2-methyl group in 2-picoline methiodide, since the latter condenses only at the 2- and not the 1-methyl group under the usual conditions, *i.e.*, a few hours at reflux temperatures. Nevertheless, after six days of reflux with 1-methylpyridinium bromide, an 82% yield of III-62 was obtained (*47*). The resemblance to the aldol condensation was pointed out by Kröhnke, who later



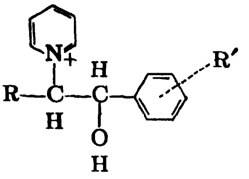
(III-61)

(III-62)

(III-63)

found that a variety of quaternary compounds with replaceable hydrogen on the carbon adjacent to the ring nitrogen atom undergo condensation. These include 1-ethyl- (*47*), 1-allyl- (*153,154*), 1-phenethyl- (*47*), 1-benzyl- (*154,156*), 1-cinnamyl- (*153*), 1-carbethoxymethyl- (*155*), and 1-phenacyl- (*32,153*) pyridinium halides. 1-Methylpyridinium halides are less reactive in this condensation reaction than 1-benzyl- or 1-phenacylpyridinium salts, which combine rapidly, even at 0°, with aldehydes in the presence of piperidine, diethylamine (*156*), or strong alkali such as sodium (*221*) or calcium hydroxides (*157*). When a phenacylpyridinium salt condenses, the alkaline conditions split out benzoate ion (III-63); the alkaline cleavage of 1-phenacylpyridinium ion is well known (*95,32,117,118,184*). Even with increased *N*-methylene reactivity as in 1-phenacylpyridinium halides, the presence of a ring methyl group leads to side reactions with dye formation (*153*). However, reaction at the 1-alkylmethylene appears to be subject to fewer structural limitations than at the 2 position.

The condensing aldehyde may be aliphatic or aromatic in the case of the phenacylpyridinium salts (*154*), but only aromatic aldehydes react with the methylpyridinium salts. In general, aromatic aldehydes have been studied with a wide variety of ring substituents and lead to pyridinium alcohols of the general type, III-64. For reactive phenacyl quaternary salts, pyridine may be replaced by a tertiary aromatic (*154*) but not aliphatic (*47*) amine.



R = H, HC=CH$_2$, C$_6$H$_5$, CO$_2$C$_2$H$_5$

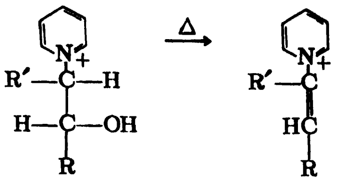
R' = *o*-, *m*-, and *p*-OH, NO$_2$, Cl, etc.

(III-64)

Alternate methods of synthesis, not necessarily more convenient, are available and have been used on occasion to confirm the nature of the reaction. Thus the quaternary compound from benzaldehyde and 1-methylpyridinium bromide is identical with that obtained from pyridine and styrene bromohydrin (*47*). The reaction of bromo alcohols is the method of choice with purely aliphatic quaternizing groups (*48*), whereas the benzaldehyde condensation appears to be very useful for the phenylethanol substituents (III-62).

Since the reactions leading to III-62 and III-64 are reversible, an excess of aldehyde is advantageous (*48,221*). On occasion, the ease of alkaline splitting of the pyridinium ethanol gave difficulty not only in synthesis (*154,155*) but also in interpreting the results, since the products dissociated into starting materials so readily as to suggest that a molecular addition product was a hand. This was true in the case of 1-nitrobenzylpyridinium halides and nitrobenzaldehydes (*156*). However, the formation of an acetate with acetic anhydride was considered evidence for the ethanol structure, and a color reaction with picryl chloride was suggested as a useful indication of successful condensation (*156,221*).

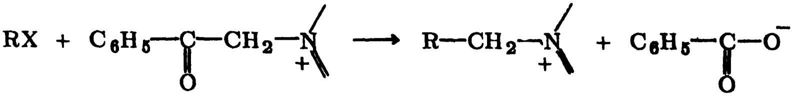
The formation of pyridinium ethanols by reduction of phenacylpyridinium salts has succeeded in a few instances with a platinum catalyst when high pressures of hydrogen were employed (*239, 240*). In general, reduction to piperidines is difficult to avoid.



(esters) (III-65)

The pyridinium ethanols give 1-vinylpyridinium salts (III-65, R′ = H) by dehydration with benzoyl chloride at 190° or acetic anhydride at 210° (*48,157*). The yields are 80–90%. In some cases milder conditions succeed. The vinyl (styryl) compound may even be obtained as a by-product in the formation of the pyridinium ethanol. This is particularly true with pyridinium salts containing an additional aromatic ring (III-65, R′ = aryl), a type that forms directly in a Perkin-type condensation of 1-benzylpyridinium bromide and its derivatives with substituted benzaldehydes in the presence of acetic anhydride and sodium or potassium acetate near 100°; the yields are good (*48,222*). Similar success was encountered with quaternary allyl- (R′ = $CH_2{=}CH{-}$) and cinnamyl- (R′ = $C_6H_5CH{=}CH{-}$) pyridinium salts (*229*).

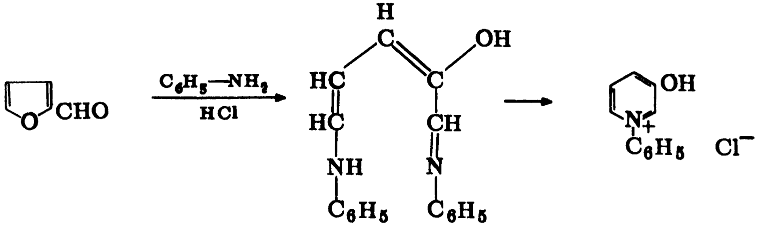
Phenacylpyridinium salts undergo alkylation with simultaneous acyl cleavage to form the homologous alkylpyridinium salt (III-66) (*228*).



(III-66)

6. By Cyclization Reactions

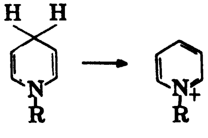
Glutaconaldehyde dianil is cyclized when heated in acid to a 1-arylpyridinium salt (III-137) (*62*). The aldehyde is generally obtained from pyridine by ring opening reactions described more fully in a later section (p. 58), but its derivatives may also be obtained from other sources. Thus furfuraldehyde, on treatment with aniline and hydrochloric acid, opens to hydroxyglutaconaldehyde dianil (III-67) which may be cyclized by heating in acid to 1-phenyl-3-hydroxypyridinium chloride (III-68) (*248,250*). Furthermore, glutaconaldehyde may be halogenated and cyclized to quaternary derivatives of 3-chloro- (*249,251*), 3-bromo- (*251*), or 3-iodopyridine (*251,252*). (*Cf.* Chapter II, pp. 280 ff. and 310 ff.)



(III-67) (III-68)

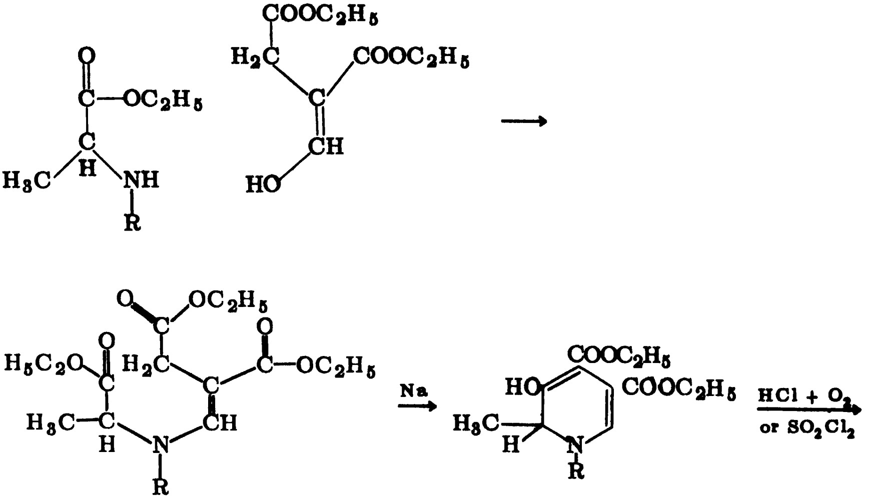
7. By Oxidation of 1-Substituted Dihydropyridines

The oxidation of dihydropyridines to pyridinium salts is a biochemical process (III-69) of vital importance (p. 51). As a preparative method it has seen little use, although it is effected by platinum catalyst, iodine, sulfur (*323*), ferricyanide (*347*), and silver ions (*318*). (*Cf.* Chapter II, pp. 230 and 236 ff.)

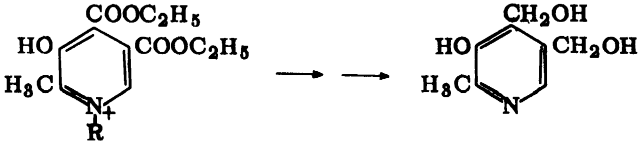


(III-69)

An interesting synthesis of pyridoxin, vitamin B_6, has been developed (*448*) in which condensation reactions lead to a 1-alkyldihydropyridine (III-70), the hydrochloride of which is readily oxidized to a pyridinium salt. The synthesis has also been successfully applied to introduce substituents into the 2 position of the vitamin (*449,450*). (*Cf.* Chapter II, pp. 534 f. and 538 f.)



(III-70)



Vitamin B_6

B. PROPERTIES AND REACTIONS

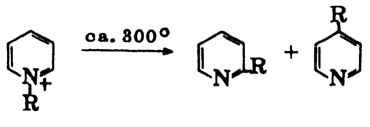
1. General Properties

Pyridinium salts are usually water-soluble compounds. Sometimes it is convenient for the sake of increasing crystallinity or altering solubility to change the anion. Conversion of an iodide to a chloride, for example, is readily achieved by treatment of a solution of quaternary iodide with silver chloride. For isolation or characterization, the perchlorates or picrates are occasionally made, although chloroferrates, which precipitate on addition of ferric chloride and hydrochloric acid to solutions of quaternary salts, are said to have many advantages (*402*). Crystalline quaternary salts containing fatty acid anions have also been prepared (*444*). A few typical salts are tabulated on p. 15.

Pyridinium compounds can be analyzed for nitrogen by the Dumas procedure; the Kjeldahl method requires modification (*286*).

Spectroscopically, the alkylation of pyridine does not alter the wavelength of maximum absorption in the ultraviolet, but an increase in intensity is observed; *i.e.*, 1-methylpyridinium chloride, λ_{max} at 260 mμ, ϵ = 10,000 in water (*481*). In alcohol, the methiodides of pyridine (λ_{max} at 260 mμ, ϵ = 4,240) and 4-picoline (λ_{max} at 255 mμ, ϵ = 6,500) have an additional peak at 225 mμ which is mainly due to the iodide ion (*293, cf.* also *275*). Too few spectra of pyridinium compounds have been published to permit generalizations. Perhaps the change in spectra of pyridine bases on quaternization is similar to that observed on acidification, namely a possible displacement of the maximum with intensification of absorption (*287*). More drastic changes in spectra occur in alkali with those quaternary salts where phenolic (*356*), amine (*106*), or alkyl (*486*) groups permit betaine, imine, or anhydrobase structures to form. An infrared study has been made of aminopyridine quaternary derivatives (*101*).

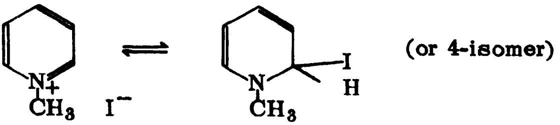
The action of heat on 1-alkylpyridinium salts may lead to a rearrangement of the 1-substituent to the 2 and 4 positions of the ring (III-71). The change is known as the Ladenburg rearrangement (*179*) and has occasional use in synthesis (Chapter V, p. 163). A different course of reaction, namely elimination, is sometimes favored by constitutional features that stabilize the double bond introduced, such as carbonyl groups or additional unsaturation. Alkyl halides may then provide olefins by way of pyridinium salt intermediates (*cf.* p. 68).



(III-71)

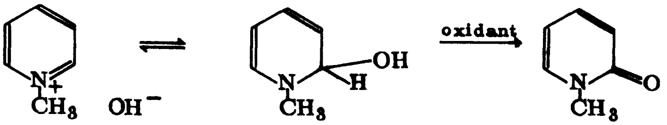
2. Pyridone Formation. Anionic Attack on the Pyridinium Ring

The failure of solutions of 1-alkylpyridinium iodides to obey Beer's law led Hantzsch to suppose that a part of the compound exists in an isomeric form containing nonionic iodine (*181*). In a more recent study of the spectral properties of 1-methylpyridinium iodide (*275*), it was estimated that the new species present in more concentrated solutions has λ_{max} at 260 mμ with a molar extinction coefficient of approximately 3500; the structure III-72 was suggested as a possibility. Subsequently it was proposed that the new species was a charge transfer complex (*446,494*), and that such complexes often precede addition of various agents to the pyridine ring, particularly to the 4 position (*493*). The effect of solvents on 1-alkylpyridinium iodide complexes has been studied (*510*).



(III-72)

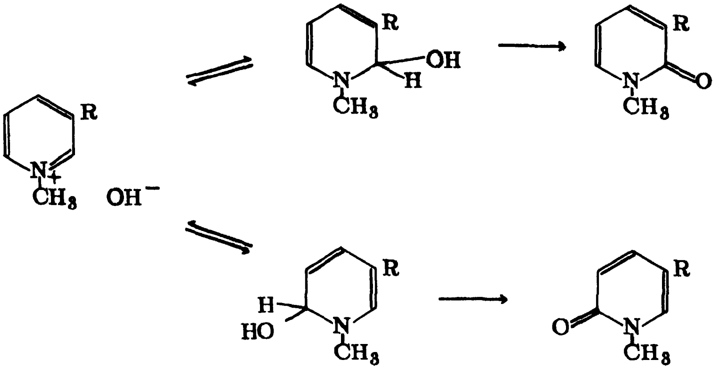
In alkaline solution, an analogous change has long been considered to take place in view of the ready oxidation to 2-pyridones (III-75) (*175,178*). In addition, quaternary hydroxides of a number of polycyclic bases are known to form a nonionic "pseudo-base" comparable to III-74. However, it appears that in the pyridinium series the equilibrium lies far in the direction of the quaternary hydroxide. Conductimetric studies on solutions of the hydroxide fail to reveal any drop in conductivity indicative of the formation of the non-ionic species to an appreciable extent (*176,177*). It is concluded, therefore, that oxidation proceeds through a very small amount of the pseudo-base present. Evidence of attack at the 2 position by hydroxide ions is also provided by a number of ring-opening reactions (p. 58).



(III-73) (III-74) (III-75)

Pyridone formation by alkaline oxidation of pyridinium compounds is a general reaction considered in detail in Chapter XII.

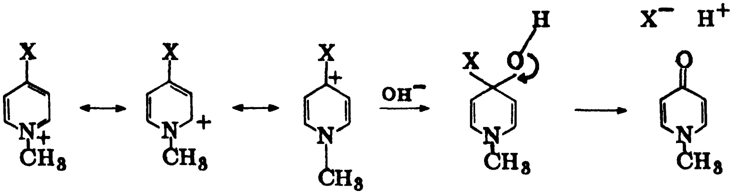
Potassium ferricyanide is the common oxidant (*180,410*). With a 3-substituted pyridinium salt, isomeric pseudo-bases are probably in equilibrium and the course of oxidation may favor either the 2 or 6 positions according to the nature of R (III-76) (*285,326*). In the important case of *N*′-methylnicotinamide, both 2- and 6-pyridones are formed in similar yield on oxidation with alkaline ferricyanide (*326*), contrary to claims of earlier investigators that only the 2-isomer formed. Similarly, re-examination of the oxidation of 3-ethylpyridine methosulfate now shows that both pyridones are formed (*460*). By contrast, trigonelline (nicotinic acid methiodide) yielded only a 6-pyridone (*285*).



(III-76)

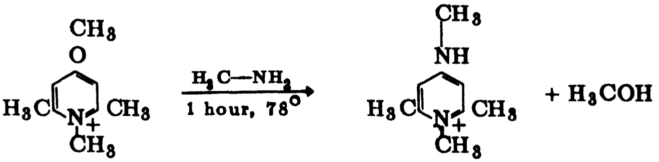
If a 2-alkyl group is present, the formation of a 6-pyridone has not been observed (*398*). Thus, it appears that anhydro base formation takes precedence, where constitutionally possible, over pyridone formation.

Pyridone formation may also reveal in some cases, in the absence of an oxidant, the susceptibility of the pyridinium ring to attack by nucleophilic agents in the 2 and 4 positions. Thus a pyridinium ion bearing a halogen (*16,182,184*) or cyano group (*514*) in the 2 position, or an alkoxy or aryloxy substituent in the 2 (*182*) or 4 (*183,188*) position, when treated with alkali, forms a pyridone directly (III-77). A similar mechanism was proposed (*44*) to explain the halogen exchange encountered during quaternization of halopyridines (p. 22). Apparently a driving force for the reaction in some cases lies in the neutralization of the pyridinium charge. While the elimination of



(III-77)

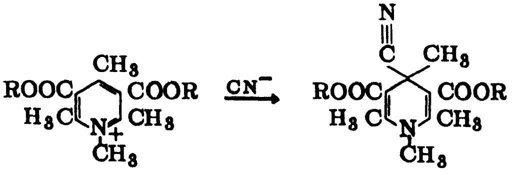
substituents has been unexpected to some investigators, the reactivity indicated has been useful in introducing thio (*243*) or amino substituents. For example, the 4-methoxy group in a pyridinium salt is readily replaced by methylamine on brief heating (III-78) (*168*). Other instances are cited elsewhere (p. 22).



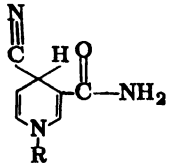
(III-78)

A variety of other anions have been shown to react with the pyridinium ring system in the 2 or 4 position. In many cases the site of reaction is ambiguous, and stable products may be isolated only in the presence of substituents which undoubtedly also influence the position of reaction.

Reaction with cyanide was demonstrated by Mumm and Hingst (*191*) with the methosulfate of collidine-3,5-dicarboxylic ester (III-79) which provided a crystalline hexane-soluble "pseudo cyanide" considered to have the 1,4-dihydro structure (III-80). The structure was based on that of the readily formed anhydro base. Deuterium exchange studies show that the nicotinamide quaternary salt "DPN" reacts with cyanide to give the 4-cyano derivative (III-81) (*334*). The



(III-79) (III-80)



(III-81)

product from nicotinamide methiodide and cyanide has been crystallized (*500*). Because of its biochemical importance, DPN (diphosphopyridine nucleotide), as well as other nicotinamide quaternary salts, has been thoroughly investigated and reaction has been noted with cyanide (*325*), hydroxylamine (*336*), strong alkali (*324*), certain carbanions derived from methyl ketones (*192,328*), and other reagents (*447*). Hydrosulfite reduction also proceeds by addition to the 4 position and is described on p. 47.

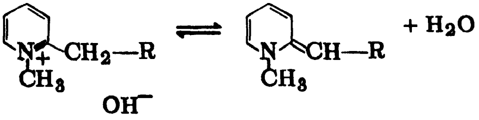
Attack at the 4 position is considered characteristic of those electron donors which readily form charge-transfer complexes according to Kosower (*493*); others substitute at the 2 position.

The reaction of the carbanion of ketones such as acetone with pyridinium salts has not been widely observed (*192,328*), but an intermediate of salt-like nature is thought to precede the formation of a carbon-carbon bond at position 4 in the ring (*497,498*).

3. Anhydro Bases

a. Methides

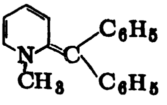
In view of their special reactivity, the anhydro bases are among the most interesting products derived from quaternary pyridinium salts. When a quaternary compound bears an alkyl group in the 2 or 4 position from which a proton may be lost, the quaternary hydroxide is in equilibrium with a non-ionic base (III-83) formed by removal of a proton from the alkyl group. These are called anhydro bases or pyridone methides. Decker (*190*) pointed out the structural features necessary for this conversion and some of the properties of the system. For example, addition of alkali to an aqueous solution of 1-methyl-2-benzylpyridinium iodide (III-82, R = C_6H_5) produced a yellow color and as the sodium hydroxide concentration rose above 20%, eventually an orange oil (III-83, R = C_6H_5) separated. Dilu-



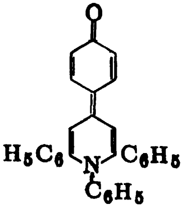
(III-82) (III-83)

tion with water led to decolorization (*190,196*). The reversal of the reaction was indicated. Thus the orange oil was soluble in benzene; when the dried yellow solution was shaken with water, the latter became immediately strongly alkaline and the benzene was decolorized. Instability of the anhydro base prevented its isolation; spontaneous decomposition to 2-benzylpyridine occurred. Conductivity measurements of aqueous solutions of 1-methyl-2-picolinium hydroxide indicate that the equilibrium is far towards the quaternary hydroxide form (*177*).

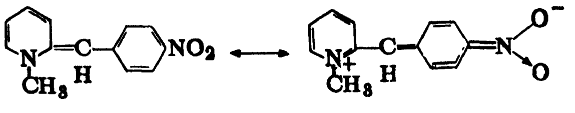
Other constitutional features may increase both ease of anhydro base formation and stability. Thus 1-methyl-2-diphenylmethylpyridinium iodide (or the 4-isomer) gives a red crystalline anhydro base (III-84) (*193*). The additional phenyl group apparently increases the stability of the methide. An *o*- or *p*-nitro group in the phenyl ring also gives rise to stable, deeply colored anhydro bases, probably owing to resonance stabilization of the conjugate base (III-85) (*196*). A further variation is the formation of a red anhydro base (III-86) from a 4-(*p*-hydroxyphenyl)pyridinium salt (*163*) which involves elimination of a proton from a phenolic group. Apparently the neutralization of the charge in a pyridinium salt may be accommodated in a variety of structures (*cf.* also *235*).



(III-84)

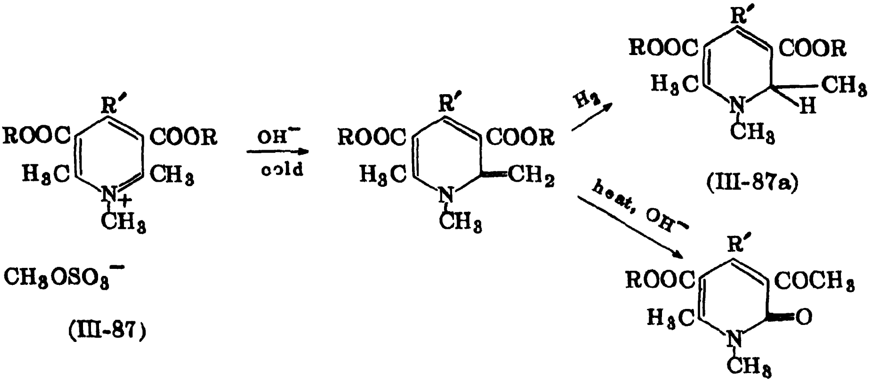


(III-86)



(III-85)

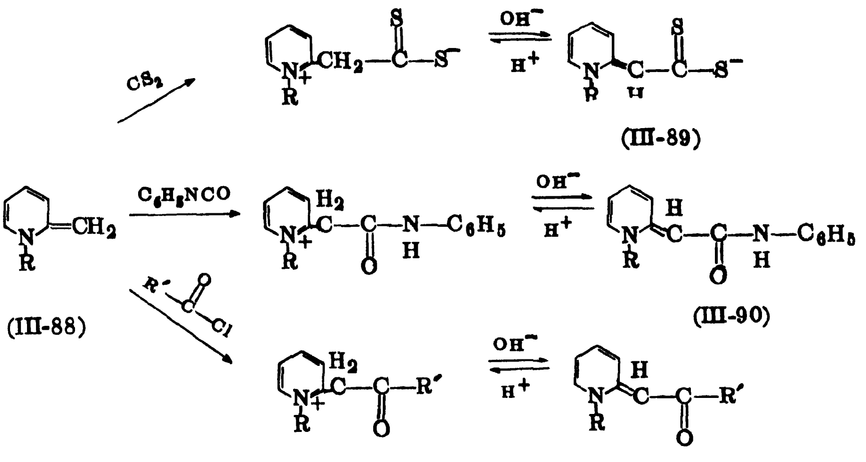
Mumm and his colleagues were the first to prepare crystalline anhydro bases, namely, those derived from 2,4,6-trisubstituted 3,5-pyridinedicarboxylic esters (III-87), and to demonstrate some of their properties (*15,191,194*). In particular, they noted the great tendency toward oxidation, partial reduction to dihydropyridines (III-87a), and alkylation on the methylenic carbon. Although the carbethoxy groups were of assistance in this work in permitting crystallization of anhydro bases, they introduced complicating side-reactions, interpreted as ring opening and recyclization to a pyridone (*15*). However, this behavior was not completely clarified (*194*).



(III-87)

(III-87a)

Pyridine anhydro bases in inert solvents react readily with a number of reagents commonly associated with the chemistry of amines, but reaction occurs at the methylene carbon atom adjacent to the ring. Thus carbon disulfide (*195*), isocyanates (*195,246*), isothiocyanates (*196*), ethoxymethylene derivatives (*234*), and some acid chlorides (*246*) lengthen the carbon chain (III-89–III-91). These reactions have not been explored extensively in the pyridine series and their generality remains to be determined. However, they appear to offer convenient routes of synthesis. Baker and McEvoy (*246*) have supplied proof of the course of the addition of phenyl isocyanate to an anhydro base of 2-picoline (III-88, R = benzyl), by transformation of the product to a known derivative of 2-piperidylacetic acid. In addition, the formation of the ketone (III-91, R′ = C_6H_5, R = benzyl) from the anhydro base and benzoyl chloride was confirmed by an alternate synthesis. It is particularly interesting that instead of isolating the anhydro base for acylation in an inert solvent, 1-benzyl-2-picolinium chloride could be benzoylated in aqueous alkali by the Schotten-Baumann procedure in a yield of



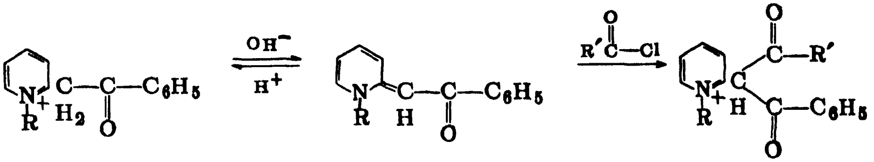
(III-89)

(III-88)

(III-90)

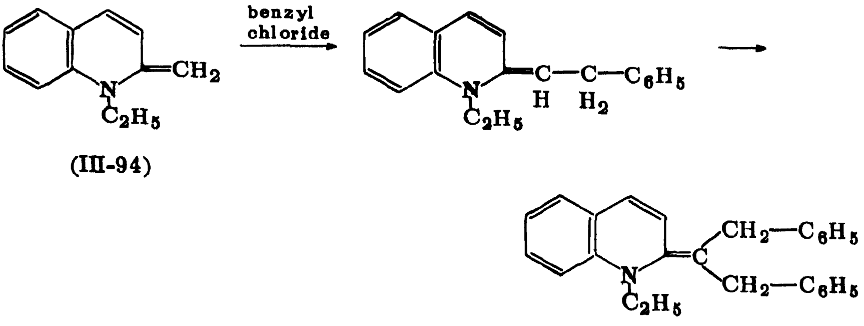
(III-91)

71% (*246*), the product precipitating as the anhydro base (III-92). This anhydro base could be further acylated with certain aliphatic acid chlorides on the methylene carbon to yield the diketone (III-93); aromatic acid chlorides favored *O*-acylation (*246*).



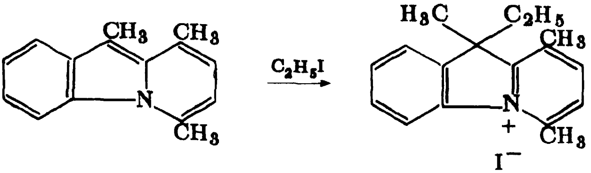
(III-92) (III-93)

While the reaction of pyridine anhydro bases with alkyl halides has been little studied (*15*), it is of interest to note some observations made in condensed pyridine systems. The anhydro base from quinaldine ethiodide (III-94), when treated with benzyl chloride in benzene, underwent *C*-alkylation to the dibenzylated derivative (III-95) (*201*). Robinson and his co-workers have demonstrated other instances of *C*-alkylation of polycyclic anhydro bases by alkyl halides (*202,203,342*). For example, the benzopyrrocoline (III-96) gave the ethylated derivative (III-97), in which a pyridinium ring is present; this behavior has been confirmed in other pyrrocoline derivatives (*388*).



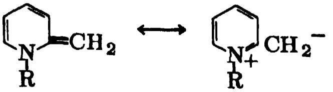
(III-94)

(III-95)



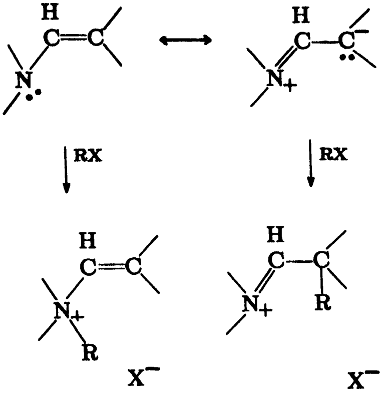
(III-96) (III-97)

The foregoing reactions of anhydro bases of pyridinium salts can be understood on the basis of resonance structure III-98 in which



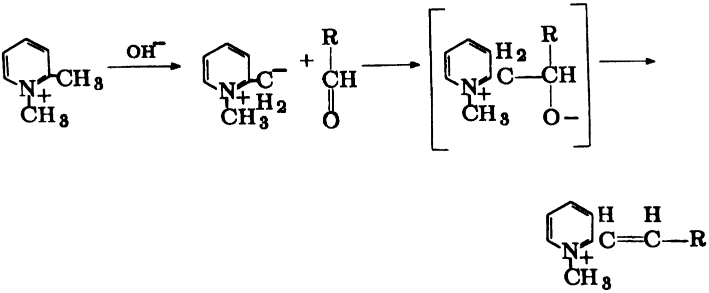
(III-98)

the unshared electron pair of the ring nitrogen atom is, in effect, accessible at the methylene carbon. This behavior of the aromatic heterocyclic bases is seen as a special instance of enamine chemistry represented by the general scheme III-99. Some purely aliphatic examples are known in which either *C*-alkylation (*281,341,496*) or *N*-alkylation (*281*) have been observed. In the pyridine anhydro bases, reaction at the nitrogen atom would result in the loss of the ring resonance energy, and consequently the methylene carbon reacts exclusively, preserving the aromatic ring.

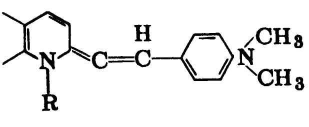


(III-99)

The condensation of aldehydes with picolinium salts has been described in an earlier section (p. 24). These are base-catalyzed and very likely involve the anhydro base in an initial attack on the carbonyl group (III-100). The interesting isolation of an allene (III-101) by Mills and Raper (*201*) is not considered an indication of a necessary mechanism (*206*). The reversibility of the aldehyde condensation reaction has been shown by alkaline hydrolysis of some stilbazole methiodides to 2-picoline methiodide (anhydro base characterized) (*196*).



(III-100)

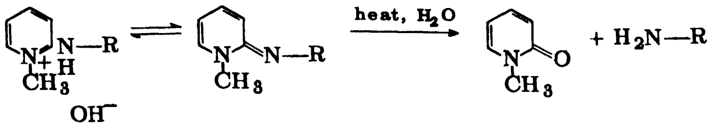


(III-101)

In contrast to the foregoing examples of reactivity, there is little evidence that picoline quaternary salts undergo the Michael reaction with any ease (*504*).

b. Pyridonimines

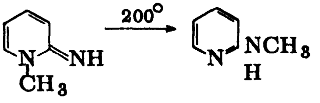
The pyridonimines are comparable to anhydro bases in that they are formed from pyridinium hydroxides by elimination of a side-chain proton, in this case from an amino group in the 2 or 4 position. The resemblance to the anhydro bases was inferred from the formation of a substance soluble in organic solvents and from the reversible color changes with pH; *e.g.*, when R = C_6H_5, III-102 is yellow



(also 4-isomer) (III-102)

(*45*). Spectral studies indicate the shift of equilibrium with pH (*106*). In addition, like anhydro bases they may be sensitive to oxidation (*87*). The base strength of pyridonimines is comparable to that of amidines, to which they bear a structural resemblance. A pK$_a$ of 12.2 and 12.5 have been recorded for 1,2-dihydro-2-imino-1-methylpyridine and its 4-isomer, respectively (*361*). In alkali, the pyridonimines undergo hydrolysis to an alkylpyridone with elimination of the amino substituent. This reaction has been very useful in determining the structure of alkylation products of aminopyridines (*87,89,104*).

Alkyl group migration has been observed in the action of heat on 1,2-dihydro-2-imino-1-methylpyridine, leading to an isomerization (III-103) to 2-methylaminopyridine (*103*). A similar change, promoted by sulfuric acid at 100°, accompanied the isomerization of 2-nitramines to 2-amino-5-nitropyridines (*90*).

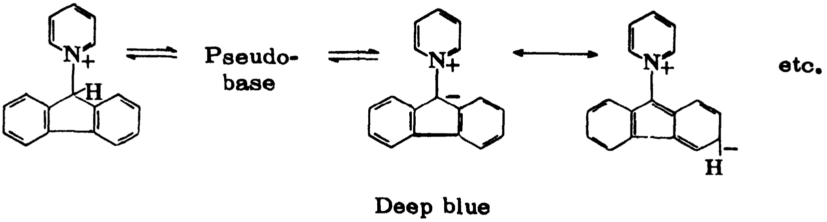


(III-103)

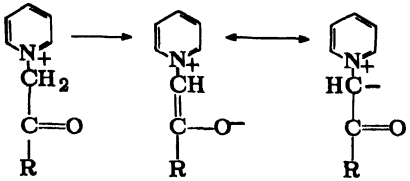
Pyridonimines are further discussed in Chapter IX.

c. Betaines. Ylides

It has been pointed out above that, in alkaline solution, a quaternary salt of a 2- or 4-alkylpyridine loses water with the formation of a molecule with no net charge, an anhydro base (III-83). Behavior similar to this is seen with some types of substituents at the 1 position of a pyridinium salt. For example, 9-fluorenylpyridinium bromide (III-104) is a colorless salt which on treatment with alkali forms a deep blue pigment, soluble in organic solvents, considered to be an anhydro base (III-105) in which the pyridinium charge is neutralized internally by a negative charge on carbon (*152,159*). The reactivity of the carbanionic site is demonstrable (*186*) by rapid nitrone formation (III-167). Other pyridinium ylides are known (*48,224,365,513*), also stabilized by distribution of the anionic charge in aromatic or pseudo-aromatic systems. *C*-Betaines (*48*) or ylides (*443*) form not only from pyridine or heterocyclic bases but also from trimethylammonium derivatives (*443*), then being less deeply colored and less stable. Resonance stabilization, with contributions from structures such as III-106, is important not only for *C*-betaines but also for other pyridinium derivatives in which the negative charge may be carried intramolecularly by oxygen or nitrogen atoms (III-107–III-109). Such compounds are generally colored and have



(III-104) (III-105) (III-106)

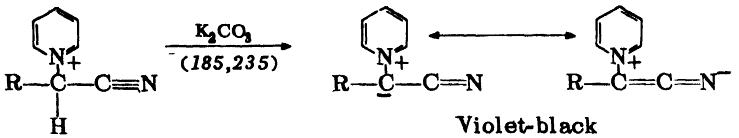


(III-107) (III-108)

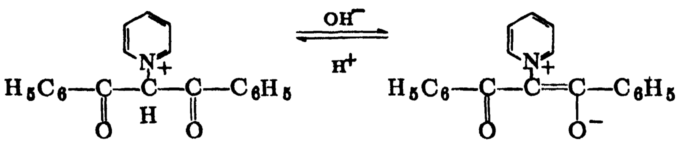
been considered analogous to the sydnones (*113*) and azulenes (*364*) in which charge separation may play an important role in color phenomena. The variation of visible color with solvent of the pyridinium cyclopentadienylide (*513*) has been interpreted as due to intramolecular charge-transfer transition (*511*).

The formation of a deeply colored compound on treatment of a quaternary pyridinium salt with alkali may on occasion indicate ring opening (p. 58). However, such products are distinguished from those under consideration here by being alkali salts, insoluble in organic solvents.

Other pyridinium salts may form betaines for which structures bearing negatively charged oxygen (III-107) or nitrogen (III-109) are important. The "enolbetaine" which is obtained from phenacylpyridinium (III-107) halides may thus have contributions of this type as well as from a structure of the carbanion type (III-108). In reviewing this area in which he and his collaborators have made so many contributions, Kröhnke considered that most enol betaines belong to either of two groups depending on whether the *O*- or *C*-betaine was the more important (*48*). In the latter case, the betaines were less stable, easily oxidized, and reactive to aldehydes, picryl chloride, *p*-nitrosodimethylaniline and other reagents. They benzoylated on the methylene carbon and had maximum absorption (*187*) in the range 440–460 mμ. The other group, containing, for example, a diacylmethane grouping (III-110), were considered mainly *O*-betaines, and were quite stable. They formed *O*-acyl derivatives,



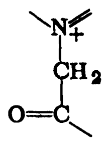
(III-109)



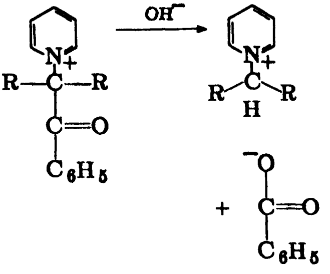
(III-110)

but were comparatively unreactive chemically and absorbed light at 320 mμ.

In a general sense, pyridinium salts containing the carbonylmethyl group as in III-111 have been compared (*48,223*) to β-diketones, since they display an active methylene in condensation with aldehydes (*153*), alkylation (*228*), acylation (*225*), color formation with picryl chloride (*227*), and coupling with diazonium salts (*148*). In addition, such quaternary salts are readily split by alkali to yield an acid and a 1-alkylpyridinium ion (III-112) (*48*). In this reaction, at least, intermediate formation of a betaine is not a prerequisite since alkylation (III-112, R = CH_3—) did not prevent cleavage even though it rendered enolization impossible (*31*). The mechanism of cleavage resembles that of β-diketones (*366*).

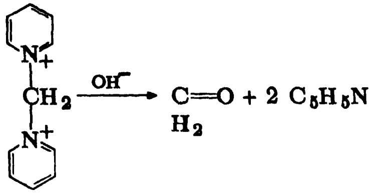


(III-111)



(III-112)

Trimethylamine will not substitute for pyridine in activating a methylene in the grouping III-111. Apparently an electron-withdrawing group is helpful in general, since the salts of dimethylaniline with phenacyl halides provide betaines of similar though less pronounced reactivity (*226*) in comparison to the pyridinium betaines. The expectation that the methylene group in methylenebispyridinium dibromide (III-113) would manifest unusual reactivity could not be confirmed because of the ease of hydrolysis of the quaternary compound to formaldehyde under alkaline conditions (*27*).



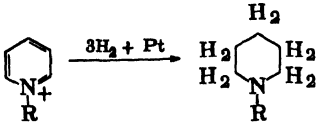
(III-113)

The analogous bis-quaternary salt from benzal bromide, on the other hand, when converted to the dihydroxide, breaks down stepwise to a betaine formally composed of equimolar pyridine and benzaldehyde (*469*).

4. Reduction

a. Reduction to Piperidines

The reduction of pyridinium salts to 1-alkylpiperidines (III-114) is generally accomplished through the use of a platinum oxide catalyst in absolute ethanol or glacial acetic acid (*278,280*). The quaternary salts are usually more readily reduced than the parent bases or hydrochlorides, and may permit certain selective reductions such as retention of a side-chain ketone group during ring reduction (*294, 279,241*). Side-chain unsaturation in conjugation with the ring is simultaneously reduced (*435*). Occasional failures to achieve reduction are encountered (*246*). Complicating features may include hydrogenolysis of a 3-hydroxy substituent (limited by addition of bicarbonate (*248*)), decarboxylation of a nicotinic acid quaternary salt (*288*), or reduction to a tetrahydro stage (*427*). Nickel catalysts have also been successfully used (*242,280*). The presence of a base, such as diethylamine, is reported to exert a favorable influence on the reduction of methiodides with this catalyst (*282*).



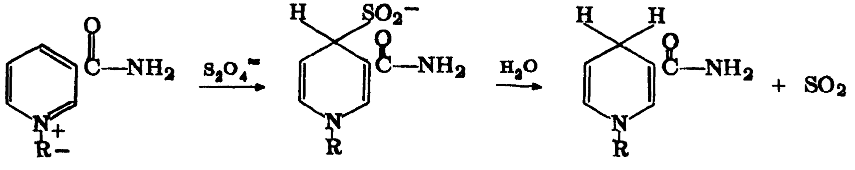
(III-114)

A number of pyridinium salts have been reduced by formic acid in the presence of potassium formate at 150–170° (*289–292*). Of interest was the formation of some tetrahydro derivative along with the completely reduced product.

b. Partial Reduction to Dihydro or Tetrahydro Pyridines

The partial reduction of pyridinium salts to dihydro or tetrahydro derivatives of known structure appears to have been successfully carried out only in a limited number of cases (reviews *299, 300*). (*Cf.* Chapter I, pp. 78 ff.) In part, the difficulty may lie in the readiness of the partly reduced structures to oxidize or polymerize unless stabilizing groups are present. Of all the chemical methods thus far applied, reduction by sodium hydrosulfite (dithionite) to dihydro derivates as studied by Karrer and his co-workers is probably the most important. With dithionite, a variety of nicotinamide quaternary salts have been converted to 1,4-dihydro products (*316*), occasionally crystallizable (*317,320,322*). Here, however, the carboxamide group exerts a stabilizing influence on the product. It may be that the carboxamide group also determines the site of reduction and that the dihydro structures formed from other pyridinium salts are different. However the low stability of 1-alkyldihydropyridines has hampered studies of these bases (*319*). Earlier studies of 1,2- and 1,4-dihydropyridines sought to avoid the stability difficulties and also limit the opportunities for tautomerization by using highly substituted derivatives. Thus, using 4-substituted derivatives of 2,6-lutidine-3,5-dicarboxylic esters, Mumm and his associates believed they prepared authentic 1,4-dihydro derivatives by thermal dismutation of the corresponding 1,1′,4,4′-tetrahydro-4,4′-bipyridines, and 1,2-dihydro derivatives by reduction of the latter (*307*) or of anhydro bases (methides) (III-87a) (*15*). The dihydro products seemed to form two groups. The 1,2-dihydro derivatives were generally yellow, were readily oxidized (silver nitrate), and did not give a blue fluorescence. In contrast, the 1,4-dihydro isomers crystallized readily, were more difficultly oxidized, and fluoresced blue. Although the products of hydrosulfite reduction were correctly interpreted as 1,4-dihydro in some cases (*314*), the generalizations misled Karrer and his colleagues into assigning the 1,2-dihydro structure to hydrosulfite-reduced nicotinamide (*316*).

Recent work establishes that, at least in the case of nicotinamide quaternary salts, the hydrosulfite reduction product is a 1,4 derivative (III-116). During the reduction an intermediate yellow color is observed which is due to the formation of a sulfinic acid (III-115, or isomer) which has been crystallized in one case (*526*). The yellow intermediate is stable in alkali, but near neutrality or in acid breaks down to the 1,4-dihydronicotinamide (III-116) (*349*). It has been proposed (*349*) that the sulfinate is the 4-isomer; however, another study favors a 2-sulfinate on the basis of maxima in the ultraviolet at 272 and 386 mμ (*526*). At moderately acidic pH values protonation at the 4 position was visualized as accompanying loss of SO_2. The structure of the hydrosulfite reduction product was determined by isotopic tracer studies on coenzymes containing nicotinamide. For example, the methiodide of nicotinamide was reduced with hydrosulfite in deuterium oxide. The deuterated reduction product on oxidation with ferricyanide provided a deuterated nicotinamide methiodide. Since the 2- and 6-pyridones formed from this quaternary salt without loss of isotope, positions 2 and 6 could not have been the original site of reduction (*347*). Only position 4 remained as a possibility.



(III-115) (III-116)

Proof that the 4 position was involved followed the synthesis of 4-deuterionicotinamide. The benzylochloride provided a crystalline 1-benzyl-1,4-dihydronicotinamide which reduced malachite green with direct transfer of deuterium. The 2 and 6 deuterated isomers were synthesized and did not transfer the isotope in this reduction (*322*).

1-Benzyl-1,4-dihydronicotinamide also reduced certain thioketones, a model of the enzymatic reduction of carbonyl groups (*509*).

In spite of the foregoing evidence, Karrer and his colleagues were loath to abandon the view that ortho-dihydro derivatives (not 1,4) are formed by hydrosulfite reduction of nicotinamide quaternary salts (*502*). As new evidence in favor of the old view, they cited the acid lability of some dihydronicotinamide derivatives in the presence of 2,4-dinitrophenylhydrazine with formation of bis-hydrazones (*501*). Ultimately, however, Traber and Karrer (*520*) agreed, on the basis of ozonization studies, that, in general, hydrosulfite reduction products, including those earlier assigned an *o*-dihydro structure, were 1,4-dihydro compounds. The acid instability of the 1,4-dihydro derivatives with hydrazone formation was interpreted as an initial isomerization to a 4,5-dihydro structure followed by ring opening. In another laboratory, evidence was obtained that the initial step was hydration to a 6-hydroxy-1,6-dihydropyridine (*531*).

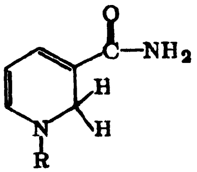
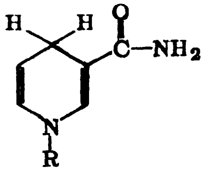
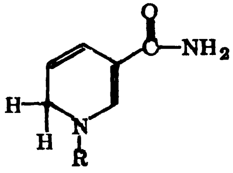
Those criteria which had been used to distinguish 1,2- or 1,6-dihydro from 1,4-dihydro structures such as fluorescence, reduction of silver nitrate, and stability to acid were recognized as unreliable (*520*). With the isolation of examples of 1,2-dihydro- and 1,6-dihydro-1-alkylnicotinamide derivatives described below, the characterization of the three isomeric systems is centering about fortunate differences in ultraviolet spectra.

Through the use of sodium borohydride, a second dihydronicotinamide product was obtained crystalline first independently by Stein and Stiassny from the 1-propylnicotinamide quaternary salt (*340*) and by Wallenfels and Schuly (*212*) from the 1-(2′,6′-dichlorobenzyl) quaternary salt. Later the 1-methyl derivative was reported (*520*). Sodium borohydride produces a mixture of 1,4-dihydro along with an *o*-dihydro in proportions that vary with structure and conditions. Occasional failure to obtain *o*-dihydro reduction (*436*) was attributed to the influence of anions on the course of reaction (*533*). (A re-examination of certain 2-dihydrodinicotinic acid derivatives claimed to have been formed earlier by Mumm (*15*) by catalytic methide reduction led to a confirmation of their structures by ozonolysis (*520*).) The new isomer was distinguished from the 1,4-dihydro by having two peaks in the ultraviolet, i.e., at 270 and 360 mμ. During the course of their studies on the properties of quaternary nicotinamide derivatives (*521–530*), Wallenfels and co-workers deduced that not only were the above two isomers formed on reduction to the dihydro stage, but also a third isomer initially detected in the mixture obtained on borohydride reduction (*522*), from which its ultraviolet spectrum was estimated by difference as consisting of a single peak near 400 mμ, a wavelength considerably longer than those found in the spectra of the known isomers. For this reason, it was concluded that the new isomer was that with the longest linear conjugated system, namely, the 1,2-dihydro form (III-116a), and that the main *o*-dihydro product obtained on sodium borohydride reduction and possessing two peaks in the ultraviolet (270, 360 mμ) had the cross-conjugated 1,6-dihydro structure (*cf.* also *520*).

A crystalline 1,2-dihydronicotinamide derivative was eventually obtained by reduction of a quaternary salt containing methyl groups in the 4 and 6 positions, *i.e.*, 1-(2′,6′-dichlorobenzyl)-4,6-dimethylnicotinamide bromide, in the hope of sterically inhibiting reduction in those positions. Sodium hydrosulfite and sodium borohydride gave the same product with a maximum absorption at 392 mμ (methanol) (*529*). Since the methyl groups shift the maximum usually about 30 mμ towards shorter wavelengths, the estimated maximum for the nicotinamide derivative itself was about 425 mμ.

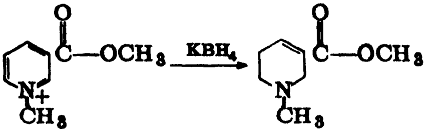
The optical properties of the isomers are summarized in III-116a.

Isomeric Dihydro Reduction Products of Nicotinamide Quaternary Salts

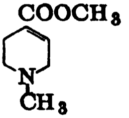
 1,2-Dihydro	 1,4-Dihydro λ_{max}	 1,6-Dihydro
425 mμ (est.)	360 mμ (H_2O), R = alkyl 340 mμ (H_2O), R = glycosidic	270, 360 mμ (H_2O)

(III-116a)

Potassium borohydride (*298*) and sodium borohydride (*427*) have been used to convert methyl nicotinate methiodide to the tetrahydropyridine arecoline (III-117), λ_{max} 214 mμ, ϵ = 10,600 in ethanol (*427*). Similarly, reduction of methyl isonicotinate methiodide to a tetrahydro derivative (III-118, λ_{max} 214 mμ, ϵ = 7,860 in ethanol) by means of sodium borohydride has been achieved in good yield (*427*). Aged Adams catalyst also gave partial reduction. Potassium borohydride is said to reduce nicotinamide nucleosides to a 1,4-dihydro stage (*301*), whereas pyridine methiodide itself reduced to a 1-methyltetrahydropyridine of uncertain structure. Perhaps conditions can be found to control the extent of reduction with these newer agents.



(III-117)

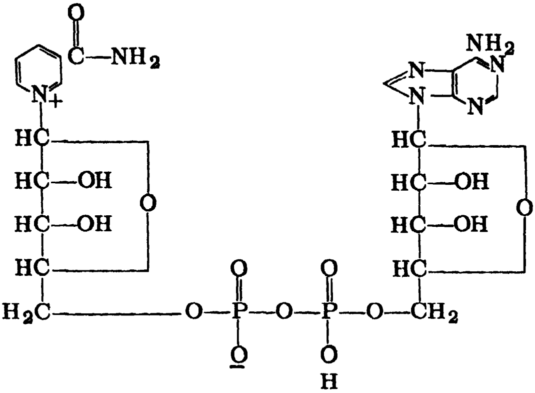


(III-118)

Sodium amalgam generally has yielded bimolecular reduction products with 1-alkylpyridinium salts (p. 55), but 1-aryl derivatives (*318*) and pyridines in which 4 substituents sterically oppose the bimolecular course (*307*) may give dihydro compounds.

c. *Nicotinamide Coenzymes*

Of paramount importance in the chemistry of the reduction of pyridinium salts are the properties of the pyridine nucleotide coenzymes. In metabolic oxidations these coenzymes accept hydrogen directly from a variety of oxidizable substrates and transfer it to other acceptors. Thus they are key metabolic catalysts. Coenzyme I has been deduced to be the pyridinium dinucleotide (III-119) by identification of the products of hydrolysis (*321*). It is commonly referred to as DPN, diphosphopyridine nucleotide. A related coenzyme, TPN or triphosphopyridine nucleotide, bears an additional phosphate group on the 2-OH group of the adenylic acid ribose. The ribosidic link to the pyridine ring is assigned the beta configuration in coenzyme I on the basis of rotational studies; an isomeric dinucleotide was subsequently isolated (*331*) in which the glycosidic link is thought to be alpha.



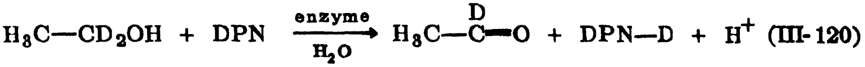
(III-119)

Even before the structure of DPN was completely known, the presence of nicotinamide as a quaternary salt was inferred. Furthermore, it had been observed that the enzymatic reduction of the coenzyme shifts its ultraviolet absorption maximum to 340 mμ. Since Karrer and Warburg found that dithionite reduction of nicotinamide methiodide gave a similar spectral shift and that the reduction product could be enzymatically reoxidized like the coenzyme, they concluded that the nicotinamide in the coenzyme was present in a quaternary linkage and that the pyridine ring was reduced in hydrogen transport (*315*).

Progress towards the synthesis of coenzyme I, diphosphopyridine nucleotide, has been hindered by difficulties in preparing the quaternary ribosidonicotinamide salt. Fischer and Raske (*160*) had studied the quaternization of pyridine itself with acetobromoglucose and obtained one crystalline and one amorphous salt. Presumably both α- and β-glucosides had formed. Later workers confirmed the formation of isomers in the quaternization of acetobromo sugars (*335,345*). Karrer and his colleagues (*317*) succeeded in preparing a crystalline glucosidonicotinamide quaternary salt but for some time were unable to obtain crystalline pentose quaternary salts. Eventually a ribopyranoside (*338*) was crystallized, but only an amorphous furanoside has been isolated (*339*). In determining the ring size of the sugar portion, evidence from the usual periodate oxidation was strengthened by reduction of the dialdehyde formed with sodium borohydride followed by acid hydrolysis (*344*). In this procedure pentose pyranosides yield only glycerol, whereas furanosides yield ethylene glycol in addition. Paper chromatography facilitated identification of the products on a micro scale. Similar studies with nicotinamide have been carried out by Haynes and Todd (*335*) who found that both *cis*- and *trans*-acetobromo sugars formed quaternary compounds. Dehydrohalogenation was a competing reaction. Of a number of hexose and pentose derivatives prepared, only the glucoside salt was crystallized. An amorphous ribofuranoside was prepared and reduced with dithionite. The product had microbiological activity.

The position of reduction of the pyridinium ring in DPN was proved by a very interesting combination of chemical and enzymatic procedures, some of which have already been discussed.

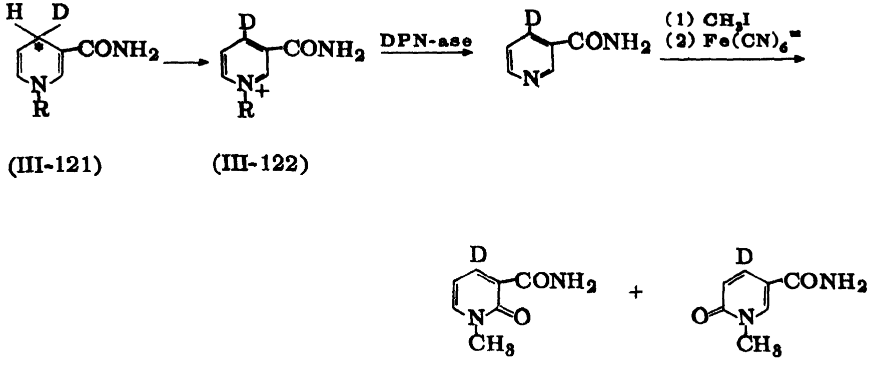
The direct transfer of hydrogen from a substrate to DPN was demonstrated in the oxidation of deuteroethanol to acetaldehyde catalyzed by alcohol dehydrogenase (III-120). The DPN took up



$$H_3C\text{—}CD_2OH + DPN \xrightarrow[H_2O]{\text{enzyme}} H_3C\text{—}\overset{D}{C}\text{=}O + DPN\text{—}D + H^+ \quad \text{(III-120)}$$

one atom of deuterium even in H_2O solution (*329*). A reduction in D_2O with ethanol as substrate gave no labelling. Therefore in the enzymatic reduction of the pyridinium ring of DPN hydrogen or deuterium was transferred from the substrate without exchange with the solvent.

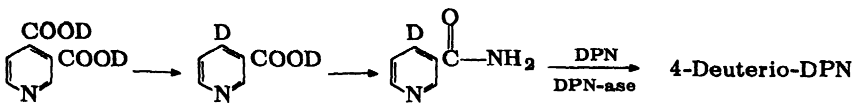
Hydrosulfite reduction in D_2O also yielded DPND (*329*). For many years DPNH had usually been written as reduced in the 2 or 6 position based on Karrer's work with model substances. However, isotopic methods have revealed that position 4 in the pyridinium ring is reduced. Thus, when DPN was labelled with deuterium by enzymatic or chemical reduction followed by reoxidation, the deuterium was not in the 2 or 6 position since it was retained during degradation to the 2- and 6-pyridones (III-123) (*327*). Of the remaining positions 3, 4, and 5, only position 4 seemed probable from considerations of structure.



(III-121) (III-122)

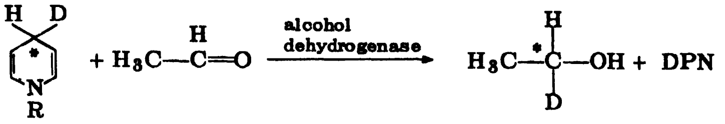
(III-123)

A direct demonstration that position 4 of the pyridinium ring is actually the site of enzymatic reduction was permitted by the synthesis of 4-deuterionicotinamide (III-124) by Mauzerall and Westheimer (*322*). This was achieved by decarboxylation of deuterated cinchomeronic acid to 4-deuterionicotinic acid, the amide of which was incorporated enzymatically into DPN (III-125) by Loewus, Vennesland, and Harris (*343*) who then showed that after chemical reduction in H_2O, the reduced coenzyme transferred the deuterium atom in the expected way to pyruvic acid. The isomeric 2- and 6-deuterio coenzymes did not transfer deuterium.



(III-124) (III-125)

An interesting development of the studies of enzymatic hydrogen transfer has been the stereospecificity of the reaction. Thus the reduction of acetaldehyde with the appropriate isomer of DPND gives an enantiomorph of 1-deuterioethanol (III-126). Its optical purity follows from the fact that on reincubation with enzyme it transfers only deuterium to DPN (*330*).



(III-126)

In contrast, another group of enzymes catalyze transfer from the opposite side of the pyridine ring and thus transfer hydrogen rather than deuterium from the above isomer (*332,333,348*). (The formula shown is not intended to represent absolute configuration.) An ionic mechanism for the action of dehydrogenases involving hydride transfer has generally been favored (*231,332,534,535*).

Agents other than hydrosulfite give indication that reduction in the 2 or 6 positions may take place in some cases. Thus sodium borohydride gave results which suggested that, in addition to the 1,4-DPNH, an isomer was formed (*311*) also absorbing at 340 mμ but less strongly.

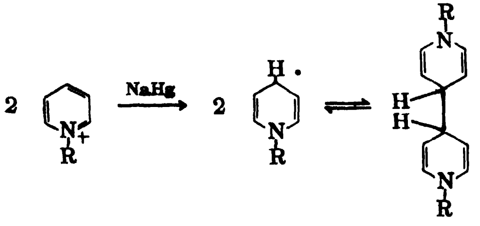
This new isomer is apparently identical with that formed by reduction of DPN electrolytically (*346,533*) or by irradiation with γ- or x-rays (*231,532*), namely, a 1,6-dihydro form, on the basis of spectroscopic relationship to model substances described elsewhere (p. 49) and is enzymatically inactive. Dimerization of the initial reduction product of nicotinamide quaternary salts obtained by such one-electron transfers has been noted (*530,533*). It has been proposed that DPN and TPN may play a role in metabolic electron transport through the dimeric reduction product (*530*) in addition to their familiar role in hydrogen transport.

d. Bimolecular Reduction Products

Hofmann observed that the reduction of 1-alkylpyridinium halides by means of sodium amalgam leads to a bimolecular product (*302*) which was shown by Emmert to be a tetrahydro-4,4′-dipyridyl (III-128) (*304*). Thus, the crystalline *N,N′*-dibenzyl derivative was readily converted to toluene and 4,4′-dipyridyl on treatment with zinc dust (*304*). The bimolecular reduction products were also formed by electrolytic reduction of alkylpyridinium salts (*303,283*).

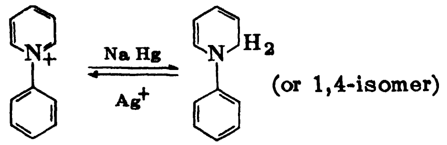
Reduction of a solution of two quaternary salts led to mixed dipyridyls in addition to the symmetrically alkylated ones (*284*).

Sodium amalgam and 1-phenylpyridinium chloride also gave some bimolecular reduction but, in contrast to the 1-alkyl salts, permitted isolation of a crystalline dihydro derivative (*306*). The *o*-dihydro structure was favored on the basis of spectra and reaction with maleic anhydride (*318*) (III-129).



(III-127) (III-128)

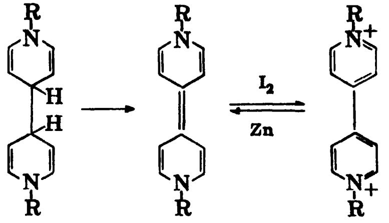
(R = alkyl)



(III-129)

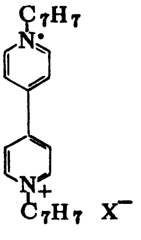
The *N,N'*-dialkyltetrahydro-4,4'-bipyridines were considered dimers of the pyridinium radical (III-127) on the basis of the colors formed on heating, the reaction with oxygen, and the oxidation by iodine to the starting quaternary salt. Some resemblance to the properties of the hexaarylethanes was noted. In those tetrahydrodipyridyls formed from 4-substituted pyridinium salts (*viz.*, 4-picoline, collidine), the dissociation is more readily observed (*307,313*). However, a stable free radical is formed only when the pyridinium nucleus bears aryl substituents which afford greater resonance possibilities (*434*).

The free radical properties at first attributed to a simple pyridine species such as III-127 (R = benzyl) were subsequently shown, chiefly by Weitz and his colleagues, to be due to bimolecular species (III-131) (*313*). Heating converted the tetrahydrobipyridyl (III-130) to the deeply colored quinonoid compound (III-131) which is brown in the solid state and blue in solution (*20*). Some consideration has been given to a di-radical resonance structure for this substance which is, however, diamagnetic (*cf.* review of Weitz (*313*)).



(III-130) (III-131) (III-132)

Oxidation with iodine leads finally to the 4,4′-bipyridinium quaternary diiodide (III-132). This is a two-electron oxidation and it is possible to obtain the intermediate one-electron stage by mixing methanolic solutions containing equimolar amounts of the bis-quaternary salt and the dipyridylene (*306*). Violet crystals are obtained which are radical ions. The monochloride has been shown to be highly paramagnetic (*312*). The monochloride (III-133) thus represents a type of radical called semiquinone by Michaelis (*433*) or meriquinone by Weitz and is distinguished from a quinhydrone-like complex (*305*) on the basis of ebullioscopic and spectral data (*313*).

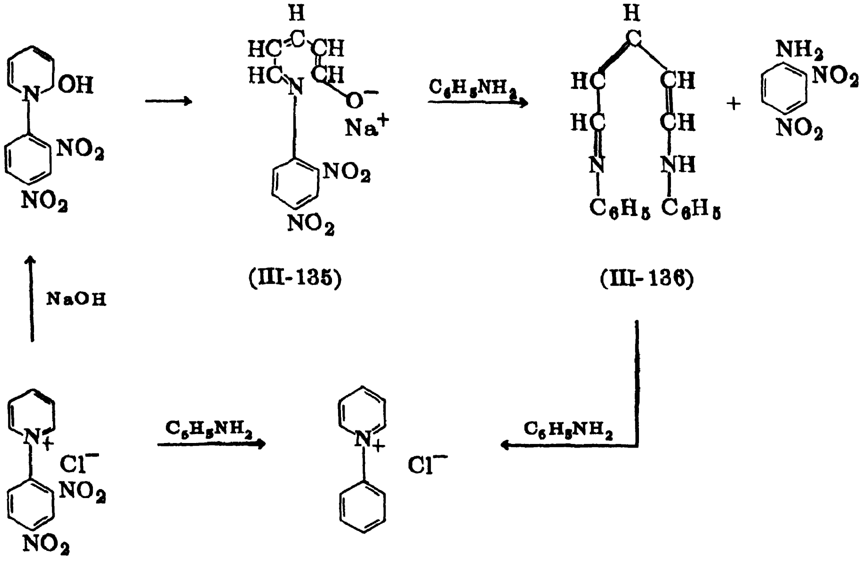


(III-133)

In the reduction of nicotinamide quaternary salts, electrolytic methods are said to lead to a 4,4′-bisdihydropyridyl (*533*), whereas a zinc and copper couple reportedly gave a 6,6′-bimolecular product (*530*). Dimerization of the initially formed radicals impedes the measurement of redox potential of this class of quaternary salts, but not that of the isonicotinic acid derivatives (*528*).

5. Ring Opening Reactions

The characteristic stability of the pyridine ring is lost when quaternization by certain agents has taken place. The behavior of 1-(2,4-dinitrophenyl)pyridinium chloride (III-134), as elucidated by Zincke and his collaborators (*61–63,253*), is typical of the labile pyridinium derivatives. It forms readily from 2,4-dinitrochlorobenzene and pyridine (*62*) and, in acid or neutral solution, is quite stable. At 150° it hydrolyzes to pyridine and 2,4-dinitrophenol (*62*). In alkali, however, a red sodium salt is formed by rupture of the ring to a derivative of glutaconaldehyde (III-135). Stabilization by resonance distribution of the anionic charge may account for the ease of ring opening not encountered in the simple 1-alkylpyridinium halides. The five carbon chain of the pyridine ring is



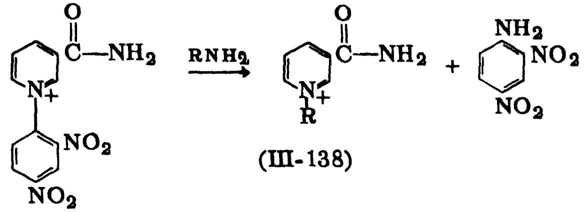
(III-135)

(III-136)

(III-134)

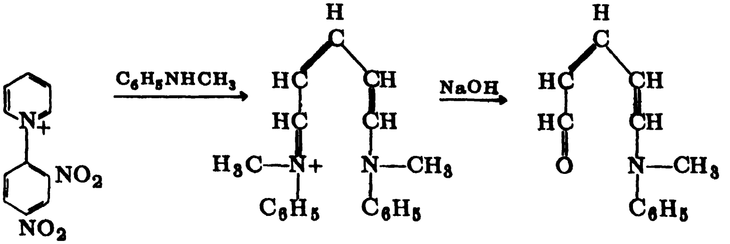
(III-137)

not readily isolated as the unstable glutaconaldehyde, but a crystalline dianil may be formed either from the red sodium salt or from the original quaternary chloride with displacement of 2,4-dinitroaniline. When the dianil (III-136) was heated with concentrated hydrochloric acid in ethanol, 1-phenylpyridinium chloride (III-137) formed. Since 1-arylpyridinium salts cannot ordinarily be obtained by direct quaternization, this reaction has preparative value. For this purpose 1-(2,4-dinitrophenyl)pyridinium chloride may be refluxed in ethanol with two moles of an arylamine until the intermediate dianil which forms has redissolved and the starting quaternary compound appears to be used up. Yields of about 60% were reported for aniline and its monochloro derivatives; nitroanilines failed to react (*62*) but have subsequently been reported to give a mixed anil in which the 2,4-dinitroaniline is retained (*273*). *p*-Hydroxy, *p*-alkoxy (*266*), and *p*-carboxy (*267*) derivatives of aniline have been successfully employed. 1-Aryl quaternary derivatives of nicotinamide (III-138) can also be prepared in this way (*268*). (*Cf.* Chapter II, pp. 280 and 313.)



(III-138)

1-(2,4-Dinitrophenyl)pyridinium chloride and a secondary amine, *N*-methylaniline, gave a dianil (III-139), in which sodium hydroxide liberated one aldehyde group (III-140) (*63*). More extensive hydrolysis resulted from acid treatment, in contrast to the recyclization

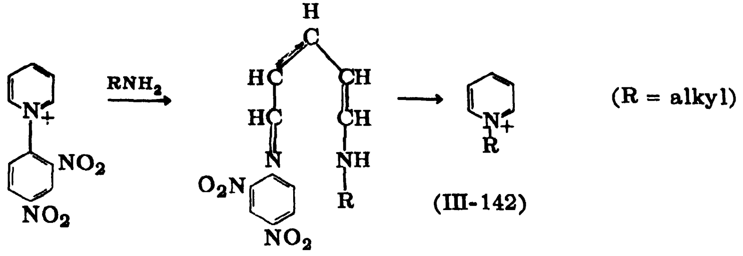


(III-139)

(III-140)

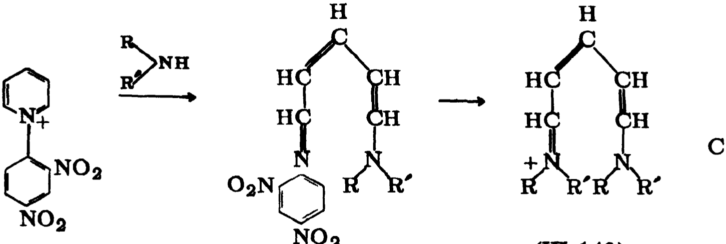
to pyridinium salts, under these conditions, of primary arylamine derivatives.

Aliphatic amines react with 1-(2,4-dinitrophenyl)pyridinium chloride less energetically than arylamines in that 2,4-dinitroaniline is less readily displaced (*253*). Instead one may initially obtain a deeply colored glutaconaldehyde mixed anil (III-141). Prolonged treatment eventually provides a 1-alkylpyridinium salt (III-142) from primary amines or a dianil (III-143) from secondary aliphatic amines (*253*).



(III-142)

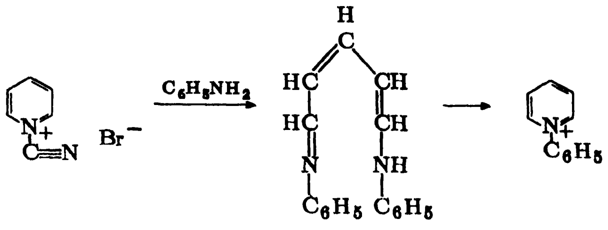
(III-141)



(III-143)

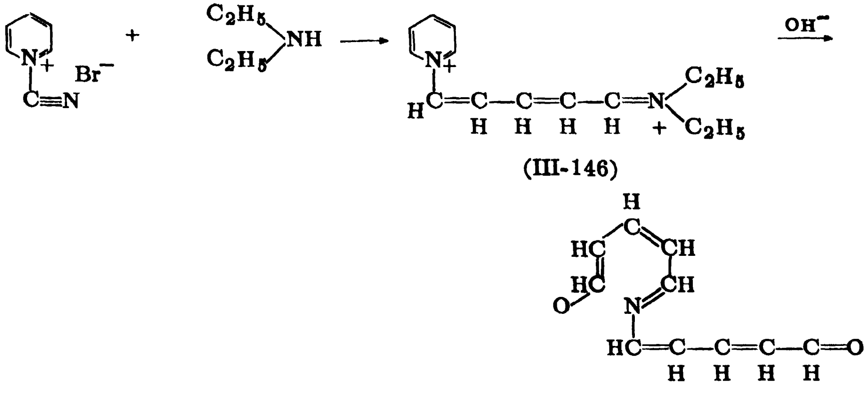
Among the substituted pyridines, a ring opening reaction of this type is limited, of course, to those bases undergoing quaternization with 2,4-dinitrochlorobenzene as discussed earlier (p. 9). The resultant quaternary compounds vary, however, in the ease of ring opening (*264,265*). Vinylogs of the 1-arylpyridinium salts, styrylpyridinium salts, also undergo ring cleavage with alkali (*232,233,459*), facilitated by electron-withdrawing groups in the aryl ring.

About the time that Zincke was exploring the 2,4-dinitrophenylpyridinium ring cleavages, König encountered similar lability in the adduct of pyridine and cyanogen bromide (III-144), preparing from the quaternary compound and aniline the known glutaconaldehyde dianil (III-145) (*254,256*). Although successful with many substituted pyridines (*274*) this reaction is subject to steric hindrance in 2,6-disubstituted pyridines and to inhibition by electronegative substituents perhaps operating to prevent the quaternization step. Glutaconaldehyde dianils from substituted pyridines occasionally have a greater tendency to recyclize to a pyridinium derivative than glutaconaldehyde dianil itself (*274*). In practice the cyanogen bromide adduct need not be isolated, but pyridine, cyanogen bromide, and an arylamine are combined in an inert solvent.



(III-144) (III-145)

When diethylamine perchlorate, pyridine, and cyanogen bromide were allowed to react, a pyridinium salt was obtained containing a glutaconaldehyde residue bound at the other end with diethylamine (III-146). This remarkable substance underwent opening of the pyridine ring on treatment with alkali, to yield the linear polyene (III-147) as a red anion. The hydrolysis could be performed step-

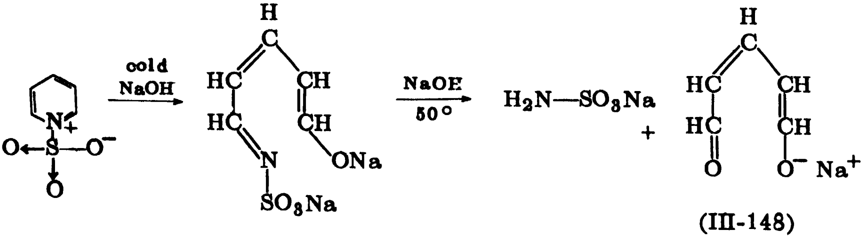


(III-146)

(III-147)

wise, first eliminating diethylamine. The changes were reversible (*270,271*).

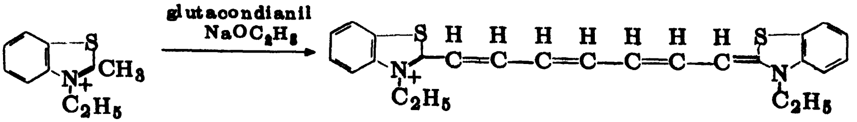
Baumgarten has shown the ease of opening the pyridine ring in the addition compounds with sulfur trioxide, chlorosulfonic acid (*261*), and ethyl chlorosulfonate. During treatment of the adduct with strong aqueous sodium hydroxide, the sodium salt of glutaconaldehyde (III-148) precipitates from solution (*260*). Application of the reaction to substituted pyridines met with difficulty (*169*). In earlier work, the prolonged action of sodium bisulfite on pyridine was found to open the ring (*258,259*).



(III-148)

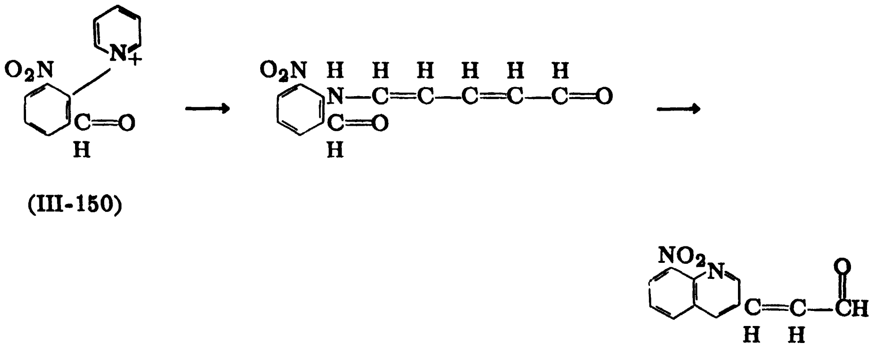
It seems probable that the pyridine ring may open under a variety of other conditions only slightly explored. For example, the halides of phosphorus gave some indication of labilizing the ring (*257*). Also, an organic acid chloride, *p*-nitrobenzoyl chloride, has promoted ring cleavage (*272*). Perhaps these reactions are more readily observed when some acceptor molecule combines irreversibly with the labilized pyridinium system. On occasion, the reaction may not give glutaconaldehyde. Thus, with chloroform and alkali, pyridine yielded cyanide and vinylacrylic acid (*151*). The same reagents acting on 2- or 4-picoline are reported to give benzenoid carbylamines (*263*). The ring opening reactions have in common very electronegative substituents at the ring nitrogen.

One of the uses of the ring opening reactions is to provide glutaconaldehyde as an intermediate for other syntheses. This purpose may be served by a solution of the sodium salt or the dianil. The latter gives aldehyde reactions; for example, cyanine dyes have been obtained from various heterocyclic quaternary compounds bearing an active methyl group (III-149) (*269*). Similarly, the dianil reacts with malonitrile or cyanoacetic ester with lengthening of the polyene



(III-149)

chain (*274*). Other active methylene compounds which have been condensed with a glutaconaldehyde monoanil include coumaranone, a pyrazolone, and oxindoles (*272*). An interesting example of the utilization of the carbon chain of pyridine for synthetic purposes has been described by Allan and Louden (*393*). 3-Nitrosalicyladehyde *p*-toluenesulfonate formed a quaternary compound with pyridine (III-150) which, when treated with aqueous alkali, underwent ring opening and recyclization to a quinoline derivative (III-151). The latter was readily converted to 8-nitroquinoline by oxidation and decarboxylation.



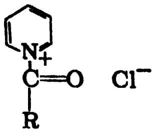
(III-150)

(III-151)

The 1-pyridylpyridinium compounds described in an earlier section (p. 11) undergo ring opening reactions that have been little studied but are apparently of the type discussed here (*70,72*).

6. 1-Acylpyridinium Halides

Acid chlorides react like alkyl halides with pyridine, but the product (III-152) has been isolated in only a few instances; its formation has generally been inferred from the structures of products isolated from reactions of acid chlorides in pyridine. However, Ad-

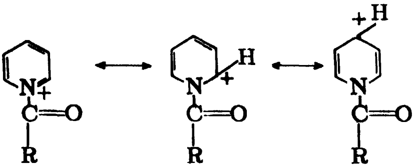


(III-152)

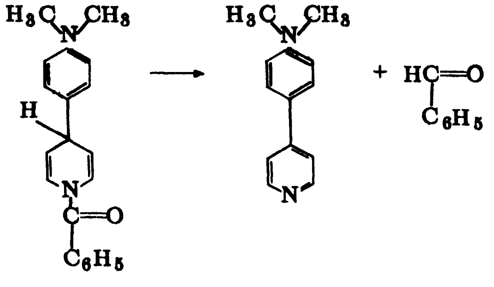
kins and Thompson (*372*) prepared solid derivatives of a number of aromatic and aliphatic acid chlorides by reaction with dry pyridine in a diluent at −20°. The product from acetyl chloride is said to be distillable (*371*).

1-Acylpyridinium halides differ from 1-alkylpyridinium halides in ease of reaction with water. Under carefully controlled conditions, high yields of acid anhydrides may be obtained (*370,372,374*). Similarly 1-benzoylpyridinium chloride was cleaved with hydrogen sulfide to form dibenzoyl sulfide. The remarkable acylating ability of acid chloride–pyridine complexes was demonstrated by Thompson by the diacylation of amides at −60°C. (*380*). However, some of these reactions are not specific for pyridine; tertiary aliphatic amines promote similar reactions.

More interesting are the reactions of 1-acylpyridinium salts which involve the pyridinium ring, reflecting the importance of structures positively charged in positions 2 or 4 (III-153). A number of 4-substituted pyridines have been isolated from various reactions of acid chlorides in pyridine. For example, dimethylaniline, benzoyl chloride, and pyridine gave 4-(*p*-dimethylaminophenyl)pyridine (III-155) and benzaldehyde, presumably by way of III-154 (*379,381*). (*Cf.* pp. 219 f.) A similar attack at the 4 position of the acylpyridinium ring by the α-methylene group of a ketone was demonstrated by Ghigi (*378*), who degraded the product obtained from pyridine, acenaphthenone, and acetic anhydride to 4-picolinic acid. This and related reactions have been clarified by Doering and McEwen (*373,377*). These

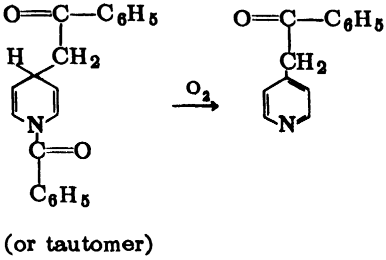


(III-153)



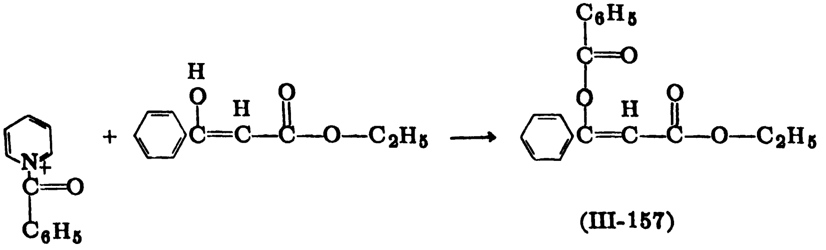
(III-154) (III-155)

authors demonstrated that the product which slowly forms at room temperature from acetophenone, benzoyl chloride, and pyridine has the structure III-156, since it is readily oxidized to 4-phenacylpyri-



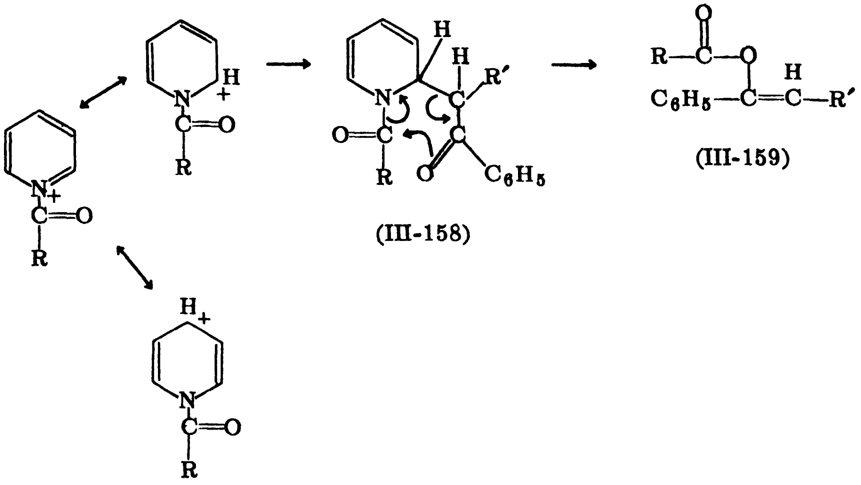
(III-156)

dine (*373*). Cyclohexanone was shown to undergo a similar reaction. β-Ketoesters did not form a pyridine substitution product but underwent *O*-acylation exclusively. For example, ethyl benzoylacetate, benzoyl chloride, and pyridine gave ethyl β-benzoyloxycinnamate (III-157). It was proposed that the formation of enol



(III-157)

esters from ketones or β-ketoesters might result from an initial combination at the 2 position leading to III-158, which rearranges rapidly to an *O*-acyl derivative (III-159). Rate studies have been offered in support of this hypothesis (*376*). Participation of the pyridine in the reaction, in contrast to other tertiary amines such as dimethylaniline, may account for the absence of *C*-acylation of β-ketoesters in pyridine (*373*). The acylation of phenols in pyridine is perhaps similar (*374*).

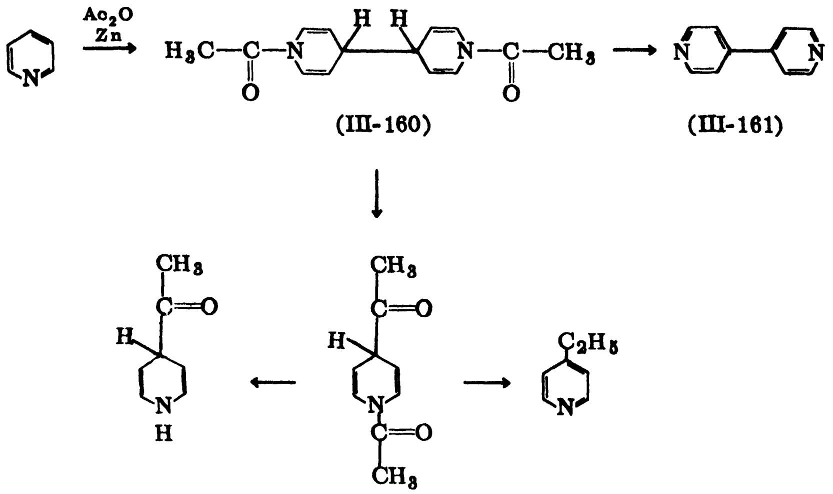


(III-158)

(III-159)

Despite this evidence of reactivity in the 2 and 4 positions, attempts to form a Reissert compound have failed (*377*). Other differences between 1-acylpyridinium and quinolinium salts have been noted (*375,381*).

Dimroth and Heene (*369*) treated a mixture of pyridine and acetic anhydride with zinc dust at 30° and obtained the bimolecular reduction product, 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (III-160), which could be oxidized by air to 4,4′-bipyridine (III-161). Further reduction to 4-ethylpyridine occurs in good yield if acetic acid is present (*357,438*). Wibaut and Arens (*357*) considered that the 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (III-160) disproportionates thermally to 1,4-diacetyl-1,4-dihydropyridine (III-162), which may be isolated if desired, and is the origin of the 4-ethylpyridine. Other 4-alkylpyridines could be prepared by this method, but the



(III-160)

(III-161)

(III-162)

yields diminished as one ascended the homologous series (*358*). In contrast to pyridine, 2-picoline (*360,432*) and 3-picoline (*432*) provided 4-ethyl derivatives in low yields.

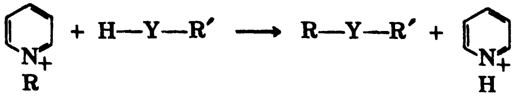
With ethyl chloroformate, pyridine, and zinc dust a similar sequence of reactions takes place and has been recommended as a route to ethyl isonicotinate (*359*).

Pyridine combines with ketene to form an unidentifiable yellow product, $C_{13}H_{11}O_3N$ (*143*), which appears to be tricyclic (*477*).

7. Pyridinium Salts of Value in General Synthetic Work

a. Alkylation

Quaternary ammonium salts are often useful alkylating agents (*458*), and pyridinium salts offer a number of examples of this type. In general the substituent at the pyridinium nitrogen atom is transferred to a suitable acceptor (III-163), such as water or alcohols (*456*), phenols (*445*), hydrogen or sodium sulfide (*309,310*), primary or secondary amines (*66,230,352,353*), mercaptans (*412*), sulfinic acids



(III-163)

(*453*), and sodium salts of organic acids (*455*). Experimental conditions for the transfers vary widely with structure. In the case of alkyl groups, the reaction has sometimes been of value by providing a more stable alkylating agent than the alkyl halide itself (*454*). When R = aryl, nitro groups in the *o*- and *p*-positions are required and arylamines (*66,352*) or ethers (*445*) may then be readily formed. Some nitroarylpyridinium salts may undergo ring opening, particularly under very alkaline conditions, but such conditions do not prevail in the reactions described here.

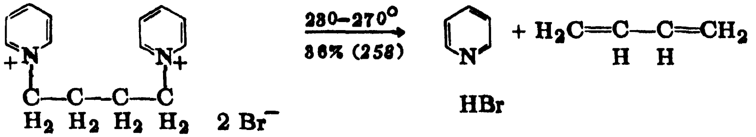
Pyridinium compounds do not alkylate Grignard reagents (*483*).

b. Introduction of Unsaturation

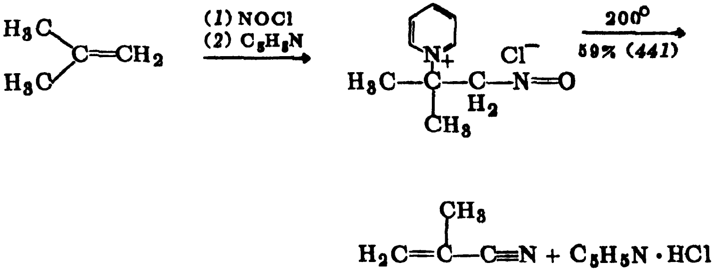
With secondary and tertiary alkyl halides, attempted quaternization with pyridine may lead merely to removal of hydrogen halide with formation of olefin. An intermediate quaternary salt need not be formed to explain this result since *s*-collidine, sterically less disposed towards quaternization, will produce elimination more readily than pyridine, very likely acting as a simple base in removing a proton. On the other hand, pyridinium salts, when heated, may break down to yield pyridine and an olefin or even an acetylene (*478*). Such reactions have been of value in the synthesis of unsaturated compounds (*48*). This elimination proceeds very readily in solution when the pyridinium ring is beta to a carbonyl (*cf.* reversible additions, p. 16). In other cases, more elevated temperatures are required. Some interesting examples are given (III-164–III-166).

c. Nitrone Formation and Uses

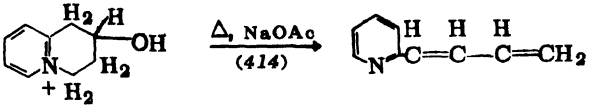
Pyridinium salts which bear a methylene group activated not only by the ring nitrogen but also by an additional group, such as carbonyl, aryl, or olefinic linkages, react readily with nitroso compounds to form nitrones. For example, phenacylpyridinium bromide and *p*-nitrosodimethylaniline combine in cold alkali (II-167) (*149,48*) with the elimination of pyridine. The virtues of the reaction, as demonstrated by Kröhnke and his collaborators, lie in the usefulness of the reactive nitrones (III-168). Thus mild acid hydrolysis provides phenylglyoxal in high yield. This synthesis has



(III-164)

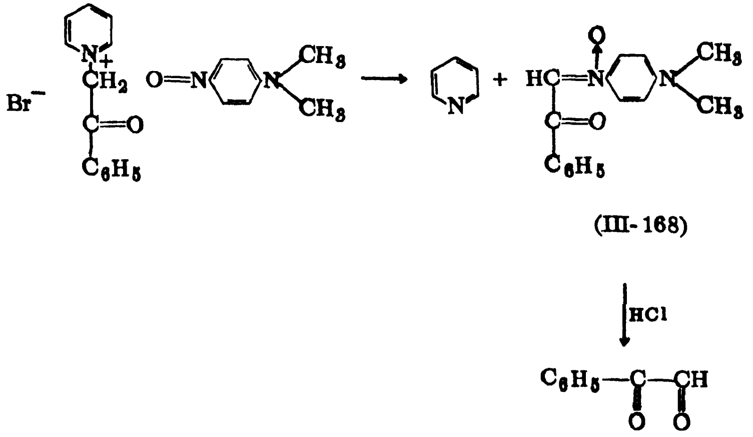


(III-165)



(III-166)

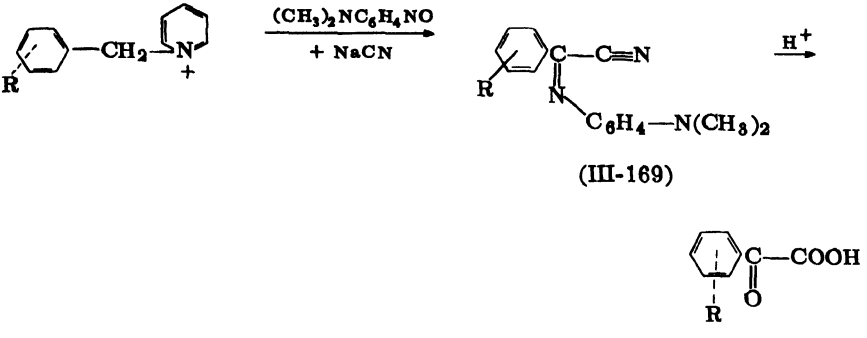
been effectively applied to obtain a variety of difficultly accessible α-ketoaldehydes, aryl or heterocyclic aldehydes, and unsaturated aldehydes (*536*) as summarized by Kröhnke (*48*).



(III-167)

(III-168)

In addition, nitrones react with cyanide to form colored anils (III-169) which are readily hydrolyzed to α-ketoacids. The nitrone need not be isolated. Thus, from benzylpyridinium salts one may obtain the anil (III-169) directly and, in some cases, hydrolyze it to the ketoacid (III-170) (*48,464*).



(III-169)

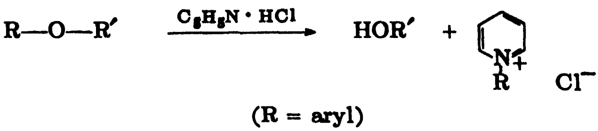
(III-170)

d. Salts and Complexes as Reagents

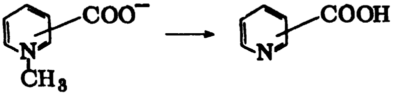
Pyridine and its homologs have been used as solvents in many reactions in which thionyl chloride, phosphorus oxychloride, and similar substances are reactants. In such circumstances, many tertiary amines also serve. Often an intermediate complex is formed which is the active agent. For example, chlorosulfonic acid in pyridine forms the pyridine–sulfur trioxide complex (*261*) which converts alcohols, even tertiary ones, to sulfate esters (*476*). It is unexpected that no compound formation of pyridine with phosphorus oxychloride is detectable (*466*) in view of the very great number of complexes that have been observed between pyridines and a host of organic and inorganic substances. Here we shall confine ourselves to a small number of salts or complexes which have value in synthesis. (*Cf.* Chapter VI, pp. 321 ff. and 326.)

Pyridine hydrochloride cleaves alkyl aryl ethers at 200° (*403–405*). *N*-Demethylation of the isomeric pyridinecarboxylic acid betaines has been achieved under similar conditions (III-171) (*471*).

(a) **Pyridine Hydrobromide Perbromide.** Pyridine forms a number of combinations with hydrogen bromide and bromine (*411*), notably pyridine hydrobromide perbromide, $C_5H_5N \cdot HBr \cdot Br_2$, m.p. 134°.



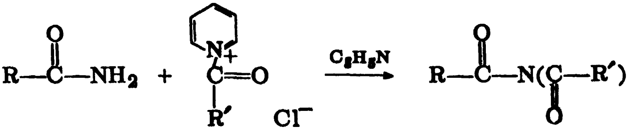
(III-171)



This product is readily obtained and quite stable (*467,408*) and is of value as a brominating agent comparable to molecular bromine (*409*). It is, however, more convenient to handle, and limited observations suggest that it offers more control, that is, less polybromination with aromatic rings (*406,407*) and greater stereospecificity in addition reactions (*452*). The reagent has been used with success in bromination of ketones (*408*).

(b) Chromium Trioxide–Pyridine Complex. A compound of the composition $CrO_3 \cdot 2C_5H_5N$ (*472*) has been useful in a number of selective oxidations. The complex is most satisfactorily formed by the addition of chromic anhydride to pyridine, appearing as a yellow solid in suspension. With this, it has been possible to oxidize primary and secondary alcohols to carbonyl compounds without attacking double bonds or thioethers (*473,474*). In addition, the oxidizing agent does not require acidic conditions that would be objectionable in some cases.

(c) Acid Chloride Complexes. In an earlier section (p. 63) the chemistry of 1-acylpyridinium halides was discussed as related to reactions of the pyridine ring. Apart from their familiar use in the Einhorn procedure for acylation, such complexes have useful acylating power less widely appreciated. For example, careful hydrolysis leads to anhydride formation (*372*). Furthermore, it has been possible to diacylate amides at low temperature (III-172) (*380*).



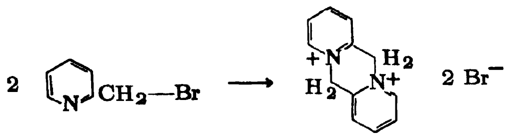
(III-172)

8. Formation of Condensed Heterocyclic Systems

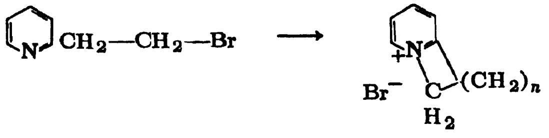
Many of the compounds found in this section are bridgehead nitrogen derivatives; this class of compounds is being treated exhaustively in a forthcoming volume in this series by W. L. Mosby.

a. Intramolecular Quaternization

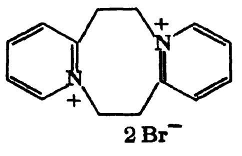
Intramolecular quaternization has been observed with 2-pyridylalkyl halides. As would be expected, the length of the side chain determines the outcome of such self-condensation reactions. Thus, in the case of 2-bromomethylpyridine, a bimolecular combination is reported to result in the formation of the tricyclic bis-quaternary salt (III-173) (*400*). 4-Bromomethylpyridine forms a polymeric quaternary compound (*465*). (Note also the self-condensation of pyridoxine (*58*).) With lengthening of the primary alkyl halide side chain to ethyl, intramolecular condensation to III-174 ($n = 1$) was claimed (*386*), but later it was shown that a dimeric structure (III-174a) was more likely the correct one (*537*). With the propyl (*391*) and



(III-173)

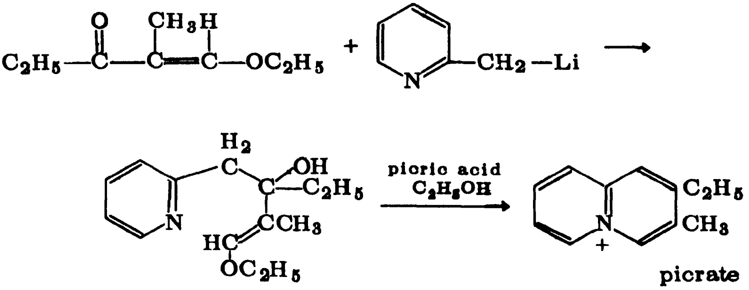


(III-174)



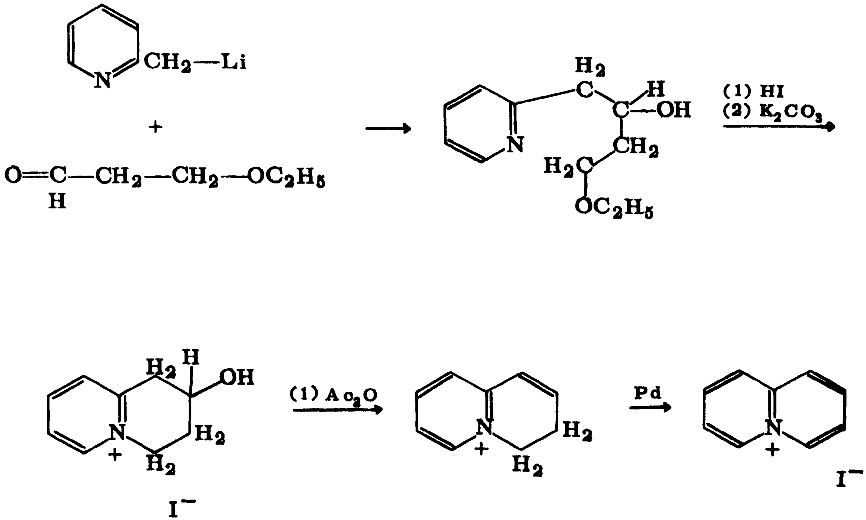
(III-174a)

butyl halides (*398*) intramolecular cyclization to salts of type III-174 ($n = 2$ and 3) is said to occur. This route to polycyclic ring systems containing pyridine has been the basis of new syntheses of quinolizinium salts: 2-picolyllithium is condensed with an appropriate alkoxymethylenic ketone or aldehyde to permit eventual dehydration and cyclization (III-175) (*419,440*). The unsuitability of this method



(III-175)

for the synthesis of quinolizinium itself led to a modification (*414*) utilizing β-ethoxypropionaldehyde and proceeding through the carbinol (III-176) to dihydroquinolizinium iodide (III-177). The latter was dehydrogenated with chloranil or palladium to quinolizinium



(III-176)

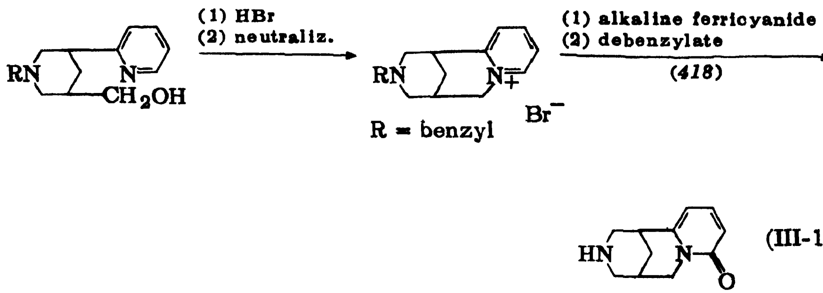
(III-177)

(III-178)

iodide (III-178). 2,6-Lutidine was carried through a similar series of transformations (*415*).

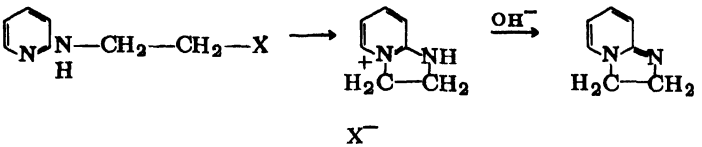
More complex pyridine-containing polycyclic systems have been prepared by syntheses embracing an intramolecular quaternization, for example, sparteine (*399*) and cytisine (*418*).

The final steps of the cytisine synthesis are given (III-179).



(III-179)

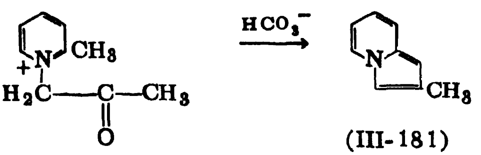
2,3-Dihydropyrimidazole (III-180) has been prepared (*413*) by an intramolecular quaternization of 2-chloroethylaminopyridine or of similar toluenesulfonates (*394*).



(III-180)

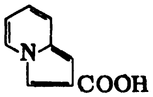
b. Cyclodehydration

(a) **Pyrrocolines.** Chichibabin discovered that the quaternary salt from 2-picoline and bromoacetone readily cyclized to an alkylpyrrocoline (III-181) on treatment with aqueous bicarbonate (*384*). α-Haloaldehydes cannot be used in this reaction, but a variety of haloketones (*368,388*), including phenacyl halides (*384,390*), lead to



(III-181)

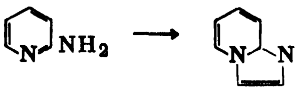
substituted pyrrocolines. 2,6-Lutidine is much less readily converted to pyrrocolines than is 2-picoline (*388*). The method has been reviewed by Borrows and Holland (*368*). Through the use of bromopyruvic ester, it was possible to prepare the 2-carboxylic acid (III-182), from which pyrrocoline itself is readily obtained on decarboxylation (*387,389*). The greater success obtained with sodium bicarbonate than stronger alkalis in the cyclization step has been related (*368*) to the probable intermediate formation of an



(III-182)

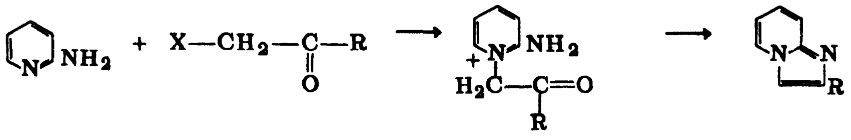
enol betaine for which cleavage by strong alkalis (p. 45) competes with cyclization.

(b) Pyrimidazoles. The formation of pyrimidazoles (imidazo[1,2-a]-pyridines) from 2-aminopyridine and α-haloaldehydes, -ketones, and -acids was introduced by Chichibabin (III-183) (*382,383*). Haloacetaldehyde, its acetals (*323*), and α-haloethers (*423*) have been used successfully.



(III-183)

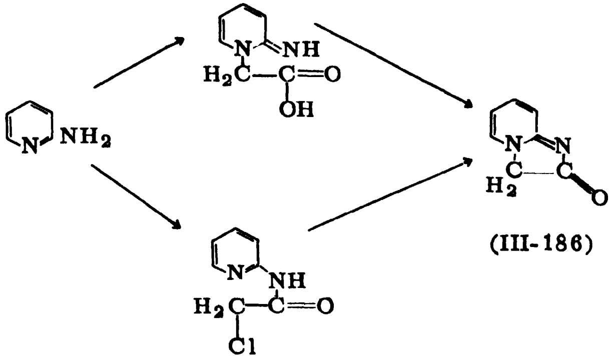
Since alkylation of 2-aminopyridine generally takes place at the ring nitrogen atom (p. 13), it has usually been assumed that in the case of the haloaldehydes and ketones, quaternization at the 1 position is the initial step (III-184) followed by cyclization to III-185. On this basis it would appear that chloroacetone and phenacyl halides



(III-184) (III-185)

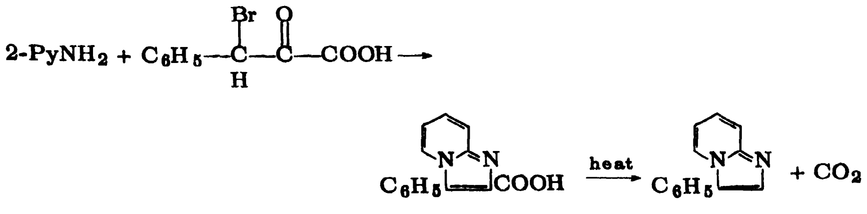
(*363*) yield a 2-methyl- or 2-phenylimidazopyridine rather than the 3-isomer. This has been confirmed (*513,515*). (When the 2-amino group is acylated, 1-carboxymethyl and phenacyl quaternary salts may undergo cyclodehydration in either of two ways according to reaction conditions (*428*).) Alkylation initially at the 2-amino group might lead to a cyclodehydration at the 3 position of the pyridine ring instead of at the ring nitrogen. Under certain conditions alkylation on the side chain can be favored, but the ultimate product is the same (*98*).

The structure of the cyclic product (III-186) obtained from 2-aminopyridine and ethyl bromoacetate is substantiated (*382*) by alternative syntheses through intermediates of certain structure.



(III-186)

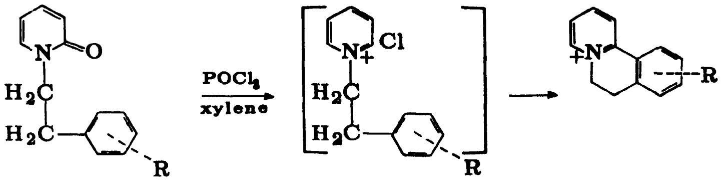
Through the use of bromopyruvic acid and its derivatives, the scope of the imidazopyridine synthesis has been extended (*395,396*). For example, the product from β-phenyl-β-bromopyruvic acid and 2-aminopyridine can be decarboxylated to yield a phenylpyrimidazole different from that obtained from phenacyl bromide and which is probably the 3-phenyl derivative (III-187) (*396*). Approaches to imidazopyridines have been reviewed by Kickhofen (*392*).



$$\text{2-PyNH}_2 + C_6H_5-\underset{H}{\overset{Br}{C}}-\overset{O}{\overset{\|}{C}}-COOH \longrightarrow$$

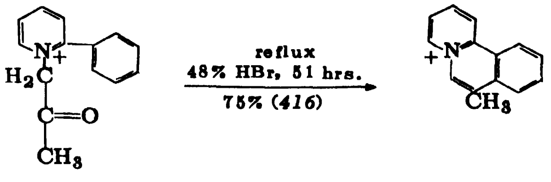
(III-187)

(c) Quinolizinium Salts. The cyclization of 1-phenethyl-2(1*H*)-pyridones to benzoquinolizinium derivatives by means of phosphorus oxychloride was devised by Sugasawa (III-188). Apparently a 2-chloropyridinium salt is formed initially (*172*). The required pyridones are readily available by ferricyanide oxidation of the quaternary salts of pyridine and phenethyl halides (*354*) or from 2-pyrones and phenethylamines (*172*). In addition to the ring closure of the unsubstituted phenethylpyridone in good yield (*425*), a number of methoxylated derivatives have been cyclized to obtain bases related to the alkaloid emetine (*354,385,424*).

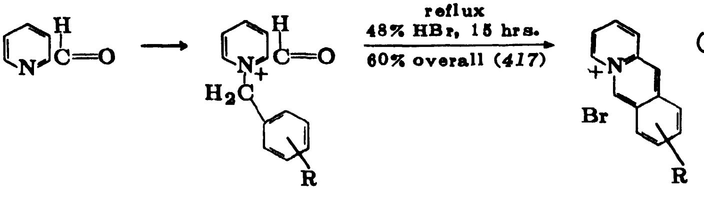


(III-188)

Cyclodehydration of suitably constituted pyridinium salts to quinolizinium salts has been achieved by Bradsher and Beavers (III-189 and III-190) (*416,417,490,516*). This ring system is also accessible by intramolecular quaternization (*cf.* pp. 72 and 224).

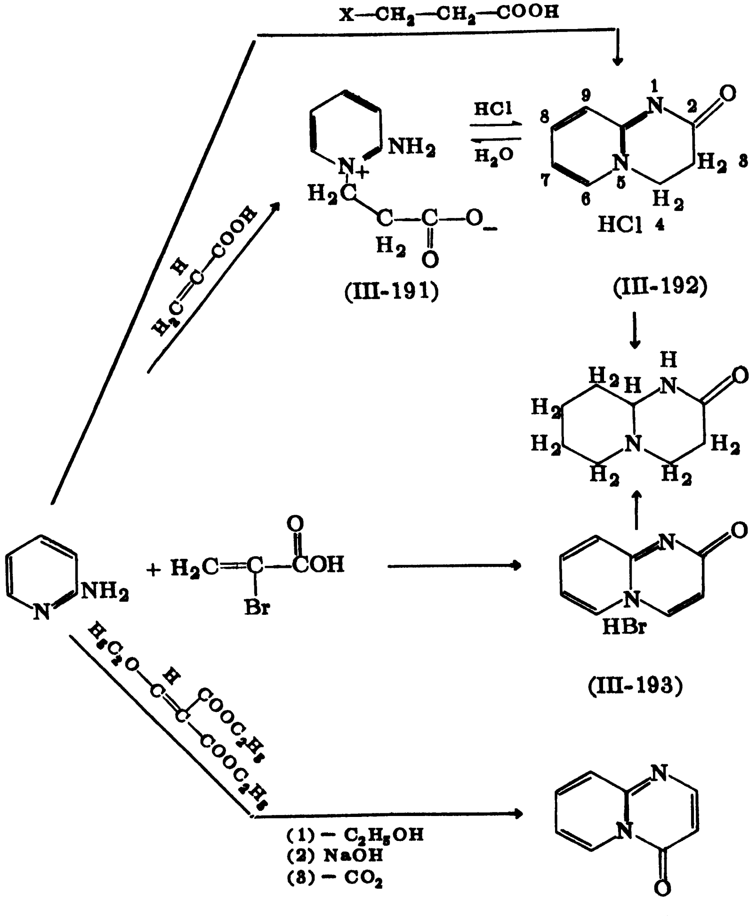


(III-189)



(III-190)

(d) Pyrido[1,2-a]pyrimidines. Prominent among the quaternization reactions of pyridines leading to new heterocyclic systems are those utilizing 2-aminopyridine. The usual uncertainty as to which nitrogen atom is alkylated prevails, and additional evidence has been required to assign structures to the cyclic derivatives obtained. Condensation of 2-aminopyridine with β-halopropionic acid or acrylic acid derivatives (*134,420*) apparently does proceed by an initial combination at the ring nitrogen atom. The bicyclic product has been shown to be 3,4-dihydro-2*H*-pyrido[1,2-a]pyrimidin-2-one (III-192) by alternate syntheses and relation to rigorously proven structures (*397*). Adams and Pachter (*134*) have demonstrated the reversible relationship of the pyridopyrimidin-2-one with the betaine (III-191) initially formed in the reaction.



(III-191)

(III-192)

(III-193)

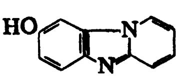
(III-194)

With 2-aminopyridine, but not with its 5-bromo derivative, propiolactone gave the same results as chloropropionic or acrylic acid (*107*). With α-bromoacrylic acid, 2-aminopyridine yields 2*H*-pyrido[1,2-a]pyrimidin-2-one (III-193) directly (*134*). When ethoxymethylenemalonic ester is used, the reaction is initiated, by contrast, on the 2-amino group leading ultimately to the isomeric pyrido-[1,2-a]pyrimidin-4-one (III-194) (*147*).

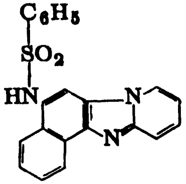
The differences in spectra of these two systems are considered valuable in assigning structures to related condensation products of 2-aminopyridines (*147*).

c. *Additions Forming Polycyclic Systems*

It has been pointed out earlier that pyridine adds to unsaturated linkages forming quaternary compounds (p. 16). Cyclization reactions may ensue. Thus, 2-aminopyridine adds to quinone with loss of water. The structure III-195 has been arbitrarily assigned (*355*). 1,4-Naphthoquinonedibenzenesulfonimide forms a similar product (III-196) with 2-aminopyridine (*135*).

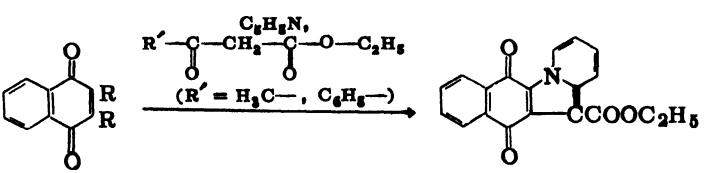


(III-195)



(III-196)

The condensation of β-ketoesters with 1,4-naphthoquinone and its 2,3-dichloro derivative in pyridine is considered to lead to the pyrrocoline derivative (III-197), presumably by way of an intermediate pyridinium salt (*112,146*). In related reactions with quinone



(R = H, Cl)

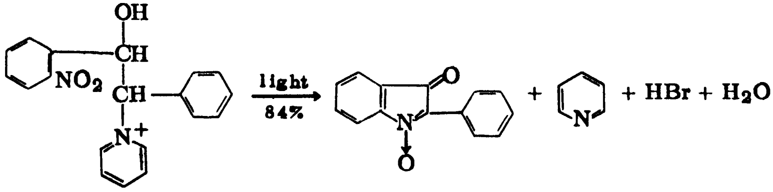
(III-197)

(*426*) and chloranil (*116*), both double bonds of the quinone ring react forming pyrrocolines.

The Diels-Alder reaction, for example, with 2-picoline and acetylenedicarboxylic ester (*140*), has led to bicyclic derivatives but appears to have little synthetic usefulness.

d. Isatogens

An interesting formation of isatogens has been observed on irradiation of appropriately substituted pyridinium salts (III-198) (*421,422*).



(III-198)

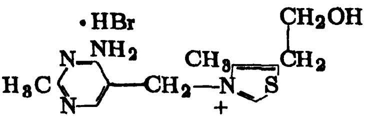
C. PYRIDINIUM COMPOUNDS OF BIOLOGICAL INTEREST

The most important quaternary pyridine derivatives occurring naturally are those of nicotinamide which have a coenzyme function. These have been discussed earlier (p. 51) and account for the role of nicotinic acid (amide) as a vitamin. The 1-methylbetaine of nicotinic acid is found in plants and is known as trigonelline (*484*).

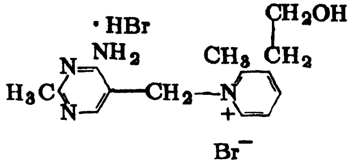
When pyridine compounds are administered to man and animals they generally undergo methylation by the active transmethylation systems and are excreted as quaternary derivatives (*482*) or 1-methylpyridones derived from them.

Many drugs containing the pyridinium ring have been prepared and found pharmacologically related to acetylcholine, a quaternary ammonium salt. Therefore, the pyridine ring has little intrinsic value in such structures. On the other hand, the biological properties of isonicotinic acid hydrazide and 3-acetylpyridine may be related to their conversion *in vivo* to unnatural pyridinium derivatives which block the nicotinamide coenzymes (*485*).

Vitamin B_1, thiamine, is a quaternary salt of thiazole (III-199). Tracy and Elderfield undertook to prepare the analogous salt (III-200), containing a pyridine ring in place of the thiazole portion. In the quaternization reaction as described (*350*), a mixture is obtained. Subsequently Wilson and Harris (*351*) found conditions for preparing the pure vitamin analog, known as neopyrithiamine (or pyrithiamine). This substance produced the first case of vitamin (thiamine) deficiency in animals by antimetabolite action (*461,462*), and has otherwise been of value in elucidating the biochemical role of the vitamin. Additional improvements in the synthesis have been reported (*352,353*). Dornow and others (*451*) have prepared various pyridinium analogs of thiamine (*463*) in an effort to relate structure and activity.



(III-199)



(III-200)

An interesting pyridinium compound of biological importance, picolinaldoxime methiodide (PAM), was evolved by Wilson as an antidote for poisoning by nerve gases such as diisopropylfluorophosphate and related pyrophosphates. These agents act by inhibiting the enzyme acetylcholinesterase. A study of the enzyme suggested that two binding sites were important in the attachment and hydrolysis of the substrate acetylcholine. The first of these, the so-called anionic site, attracted quaternary ammonium salts and remained unblocked when the enzyme was inhibited (*308*). Inhibition apparently consisted in phosphorylation of a second site, the esteratic site, where hydrolysis normally proceeded (*337*). Hydrolytic removal of the phosphorus from the enzyme permitted reactivation (*262*), but the process was slow. Bifunctional molecules were accordingly designed which would serve as an antidote by utilizing the anionic site for attachment to the enzyme and by providing a nucleophilic group to displace the bound phosphate. Picolinaldoxime methiodide was one of the structures thus arrived at and proved effective in protecting animals against lethal doses of acetylcholinesterase poisons (*362*).

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CHAPTER IV

Pyridine *N*-Oxides

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Pyridine behaves towards per-acids in a manner characteristic of tertiary amines in general. The unshared pair of electrons of the nitrogen atom binds an oxygen atom in a coordinate linkage, forming an amine oxide (IV-1). The new bond is represented as an arrow which suggests the origin of the bond electrons and is used interchangeably with the dipolar representation (IV-2) which indicates the polar character of the resultant link. In contrast to aliphatic

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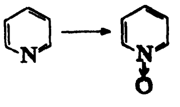
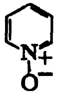

(IV-1)


(IV-2)

and aromatic amine oxides, however, the opportunities for resonance interaction in the planar pyridine 1-oxides result in profound alterations in the chemical behavior of the ring and of substituents that may be attached to the ring. These effects are of considerable theoretical importance in the chemistry of the aromatic heterocyclic amines. Moreover, a new and powerful degree of control in certain synthetic procedures is afforded by the *N*-oxide grouping. Since the oxygen atom may be removed by reduction or by the reaction conditions themselves subsequent to the change in which its influence was exerted, the oxygen may be regarded as a temporary addition to the molecule for guiding reactions, such as substitution or displacement. The exploration and exploitation of these possibilities is a rather recent development in pyridine chemistry, which has removed pyridine 1-oxide from the obscurity that befell it for some years following the initial synthesis by Meisenheimer (*1*).

A. PREPARATION

Two main methods of preparation for pyridine oxides have been used. Pyridine and many of its derivatives have been directly converted to 1-oxides by means of per-acids (Table IV-1). Alternately, starting with an oxide, one may introduce or change substituents in the ring with retention of the 1-oxide grouping (Table IV-2, pp. 104 ff.).

1. Direct Oxidation

Perbenzoic acid was used by Meisenheimer for the oxidation of pyridine itself (*1*). Many other pyridines have subsequently been converted to their oxides by means of this agent. The perbenzoic acid is usually prepared as a chloroform solution (*84*) to which the pyridine is added. The reaction is allowed to proceed at room tem-

TABLE IV-1. Pyridine 1-Oxides Prepared by Direct Oxidation

Oxide	M. p., °C.	Boiling point		M. p., °C.		Oxidant	Conditions	Yield, %	Ref.
		°C.	mm. Hg.	Hydrochloride	Picrate				
Pyridine 1-oxide	66	138–40	15	180–81	179.5	perbenzoic acid	room temp.		1
						peracetic acid	85°	80	117
						H_2O_2, HOAc	70°, 12 hrs.		23,57
2-Picoline 1-oxide						perphthalic acid	ether	71	17
		127	12	125	125–26.5	H_2O_2, HOAc	70–80°, 12 hrs.	80	42,72,79
3-Picoline 1-oxide		146–49	15		138–39				72
	33–36	156–58	16		141–43	H_2O_2, HOAc	70–80°, 12 hrs.	77	79,72,91
4-Picoline 1-oxide	186–88	151–53	11		158.7–60	H_2O_2, HOAc	70–80°, 12 hrs.	73	72,73, 79,19
2,3-Lutidine 1-oxide	85–93					H_2O_2, HOAc	80–90°, 6 hrs.		152
2,4-Lutidine 1-oxide				178	140	perphthalic acid	ether sol'n.	71	17
2,6-Lutidine 1-oxide				219.5		perphthalic acid	ether sol'n.	41	17
		115–19	18		127.5–29	H_2O_2, HOAc	70–80°, 12 hrs.	75	72
2,4,6-Collidine 1-oxide				246	166–67	perphthalic acid	ether sol'n.		17
2-(*p*-Anisyl)pyridine 1-oxide	135–36				136–38	perbenzoic acid	0°, 40 hrs.	70	36

(continued)

TABLE IV-1. Pyridine 1-Oxides Prepared by Direct Oxidation (*continued*)

Oxide	M. p., °C.	Boiling point		M. p., °C.		Oxidant	Conditions	Yield, %	Ref.
		°C.	mm. Hg.	Hydrochloride	Picrate				
2-*n*-Butylpyridine 1-oxide		not isolated				H_2O_2, HOAc	70–80°, 12 hrs.		72
2-Ethylpyridine 1-oxide		109–13	4			H_2O_2, HOAc			73
5-Ethyl-2-methylpyridine 1-oxide		147	11			H_2O_2, HOAc			73
		93	0.2		106–107.2	H_2O_2, HOAc	100°, 3.5 hrs.	92	115
2-Phenylpyridine 1-oxide	155–55.5				150–52	perbenzoic acid	0°, 40 hrs.	77	36
4-Phenylpyridine 1-oxide	151–52					H_2O			
2,6-Diphenylpyridine 1-oxide	125–26				161–62	perbenzoic acid	room temp., 3 days	14	36
2,4,6-Triphenylpyridine 1-oxide	184			171–72	189	perbenzoic acid	45°, 36 hrs.	10	1
2-Acetamidopyridine 1-oxide	130–31					peracetic acid	7 hrs., 50–70°	85	75
3-Acetamidopyridine 1-oxide	215.5–16.5					H_2O_2, HOAc		26	124
2-Acetamido-6-methylpyridine 1-oxide	123–24					peracetic acid	7 hrs., 50–70°	76	75
3-Acetylpyridine 1-oxide	142					H_2O_2, HOAc	70°, 10 hrs.	80	69
4-Acetylpyridine 1-oxide	132					H_2O_2, HOAc	70°, 10 hrs.	95	69

2-Benzyloxypyridine 1-oxide	103–106					perbenzoic acid	room temp., 3 days	45	30
2-Benzyloxy-5-bromopyridine 1-oxide	127–28					perbenzoic acid	room temp., 3 days	25	31
2-Benzyloxy-4-methylpyridine 1-oxide	81–82					perbenzoic acid	room temp., 3 days	53	31
6-Benzyloxy-2-methylpyridine 1-oxide	99–100					peracetic acid	55–80°, 10 hrs.	66	76
4-Benzyloxypyridine 1-oxide	178–79				123–4	perbenzoic acid	room temp., 3 days		30
2-Bromopyridine 1-oxide				135–36		perbenzoic acid	room temp., 4 days	60	32
						40% peracetic acid	45–50°, 1 day	70	32
3-Bromopyridine 1-oxide				181–82	139–41	perphthalic acid	10 days, 0°	40	21,22
		143–48	4			H_2O_2, HOAc	75°, 12 hrs.	85	19,39, 131
2-Bromo-3-ethoxypyridine 1-oxide				159–60		perbenzoic acid	room temp., 4 days	52	32
3-Bromo-5-methoxypyridine 1-oxide	200–201					perbenzoic acid	room temp., 4 days	90	116
2-Bromo-3-methylpyridine 1-oxide				179–80		perbenzoic acid	room temp., 4 days	67	32
2-Bromo-4-methylpyridine 1-oxide				147–48		perbenzoic acid	room temp., 4 days	59	32
2-Bromo-5-methylpyridine 1-oxide				141–42		perbenzoic acid	room temp., 4 days	64	32

(continued)

TABLE IV-1. Pyridine 1-Oxides Prepared by Direct Oxidation (*continued*)

Oxide	M. p., °C.	Boiling point		M. p., °C.		Oxidant	Conditions	Yield, %	Ref.
		°C.	mm. Hg.	Hydrochloride	Picrate				
2-Bromo-6-methylpyridine 1-oxide				185–86		perbenzoic acid	room temp., 4 days	61	32
2-Chloropyridine 1-oxide				138–42		peracetic acid			138
2-Chloro-3-methylpyridine 1-oxide				146–50		peracetic acid			138
2-Chloro-4-methylpyridine 1-oxide				121–25		peracetic acid			138
2-Chloro-5-methylpyridine 1-oxide				125–28		peracetic acid			138
2-Chloro-6-methylpyridine 1-oxide				155–60					138
2-Chloro-4,6-dimethylpyridine 1-oxide				144–48					138
3-Cyanopyridine 1-oxide									39
2,6-Diacetamidopyridine 1-oxide	212–13					peracetic acid	7 hrs., 50–70°	79	75
2,5-Dibromopyridine 1-oxide				165–66		perbenzoic acid	room temp., 4 days	6.5	32
3,5-Dibromopyridine 1-oxide	143–44.5					perbenzoic acid	room temp., 4 days	80	28
3,5-Diethoxypyridine 1-oxide	115.5–16.5				114.5	perbenzoic acid	room temp., 4 days	85	28
3,5-Dimethoxypyridine 1-oxide	91–93				131–32	perbenzoic acid	room temp., 4 days	25	116

2,6-Dimethoxy-4-methylpyridine 1-oxide	68–69			perbenzoic acid	room temp., 18 hrs.	5	114
2-Ethoxypyridine 1-oxide				30% H_2O_2, HOAc	60°, 4 days		24
	71–73		111–13	H_2O_2,HOAc			33
3-Ethoxypyridine 1-oxide		perphthalate 83–84		perphthalic acid	room temp., 4 days	30	24
2-Ethoxy-3-methylpyridine 1-oxide				H_2O_2, HOAc	56°, 19 hrs.		34
2-Ethoxy-4-methylpyridine 1-oxide	101–102		139	peracetic acid	45°, 24 hrs.	30	34
2-Ethoxy-6-methylpyridine 1-oxide	102–103		88–89	H_2O_2, HOAc	56°, 19 hrs.		34
Ethyl isonicotinate 1-oxide	68–70		187	perphthalic acid		70	89
Ethyl nicotinate 1-oxide	99.5			H_2O_2, HOAc	100°, 3 hrs.	50	35
3-Hydroxypyridine 1-oxide	189–91			perbenzoic acid	room temp., 1 day	65	30
Isonicotinic acid 1-oxide	272						79,9
2-Methoxypyridine 1-oxide		115 (dec.)	145–46.5	perbenzoic acid	room temp., 4 days	60	95
3-Methoxypyridine 1-oxide		128	160–61	perbenzoic acid	room temp., 4 days	85	95
Nicotinamide 1-oxide							74
Nicotinic acid 1-oxide	254 249 (dec.)			H_2O_2, HOAc	100°, 3 hrs.	70–80°	35,79
Picolinic acid 1-oxide	161						58,79, 80

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides

Compound	M. p., °C.	M. p., °C.		Starting material	Conditions	Yield, %	Ref.
		Hydrochloride	Picrate				
2-Acetamido-4-nitropyridine 1-oxide				2-acetamidopyridine 1-oxide			92
3-Acetamido-4-nitropyridine 1-oxide				3-acetamidopyridine 1-oxide			92
4-Acetamido-2-nitropyridine 1-oxide				4-acetamidopyridine 1-oxide			92
4-Acetoxy-3-methylpyridine 1-oxide	220			4-nitro-3-picoline 1-oxide	Ac_2O, 100°, dimethylaniline	65	134
2-Aminopyridine 1-oxide	161–63	153–56		picolinamide 1-oxide	Hofmann degradation	50	58
	164–65			2-acetamidopyridine 1-oxide	10% NaOH, 100°, 4 hrs.	76	75
				2-dibenzoylaminopyridine 1-oxide	hydrolysis		93
3-Aminopyridine 1-oxide				3-acetamidopyridine 1-oxide	10% NaOH, 100°		124
	121–23			3-bromopyridine 1-oxide	NH_4OH, 130°	59	131
4-Aminopyridine 1-oxide		180	199	4-nitropyridine 1-oxide	$(NH_4)_2S$, hot		14
				4-nitropyridine 1-oxide	Pd, H_2 in 10% HCl		57
	235–36				Pd-$SrCO_3$, EtOH, 60°	78	163

2-Amino-3-methylpyridine 1-oxide	128–29			2-amino-3-picoline	Ac_2O, peracetic acid then NaOH	65	138
2-Amino-4-methylpyridine 1-oxide	130–32			2-amino-4-picoline	as above	72	138
2-Amino-5-methylpyridine 1-oxide	150–51			2-amino-5-methylpyridine	as above	75	138
2-Amino-6-methylpyridine 1-oxide	153–54			2-amino-6-methylpyridine	as above	78	138
				2-acetamido-6-methylpyridine 1-oxide	10% NaOH, 100°, 4 hrs.	85	75
2-Amino-4,6-dimethylpyridine 1-oxide	149–50			2-amino-2,6-dimethylpyridine	Ac_2O, peracetic acid, then NaOH	70	138
4-Amino-5-ethyl-2-methylpyridine 1-oxide	200–203 209–12		177.5–81.5	4-nitro-5-ethyl-2-methylpyridine 1-oxide	30% Pd-C, EtOH	100	115
4-Amino-2-methylpyridine 1-oxide		189–91		4-nitro-2-methylpyridine 1-oxide	60% Pd-C, 10% HCl		41
4-Amyloxypyridine 1-oxide			87–88	4-nitropyridine 1-oxide	amyl alcohol, $C_6H_5NO_2$	26	45
4-Benzyloxypyridine 1-oxide	175–76			4-nitropyridine 1-oxide	Na benzylate	80	54,57

(*continued*)

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides (*continued*)

Compound	M. p., °C.	M. p., °C. Hydrochloride	M. p., °C. Picrate	Starting material	Conditions	Yield %	Ref.
4-Benzyloxy-2-methylpyridine 1-oxide	160–61			4-nitro-2-methylpyridine 1-oxide	Na benzylate		67
4-Benzyloxy-3-methylpyridine 1-oxide	181 (hydrate)		185	4-nitro-3-methylpyridine 1-oxide	Na benzylate		134
6-Benzyloxy-2-pyridineacetic acid 1-oxide	147–51			6-benzyloxy-2-pyridinepyruvic ester	NaOH, H_2O_2, 36 hrs.	36	76
2-Benzylthiopyridine 1-oxide	168–69			2-bromopyridine 1-oxide	$NaSCH_2C_6H_5$, 50° EtOH	46	32
4-Bromopyridine 1-oxide	142–43		142	4-nitropyridine 1-oxide	HBr, HOAc, 120°, sealed tube	70	23
	163			4-aminopyridine 1-oxide	Sandmeyer reaction	30	54,57
	162–63			4-chloromercuripyridine 1-oxide	Br_2		66
			223–24	4-nitropyridine 1-oxide	48% HBr, 160°, urea, sealed tube		55

3-Bromo-5-methoxy-6-nitropyridine 1-oxide	164.5–66		3-bromo-5-methoxypyridine 1-oxide	H_2SO_4, KNO_3, 30–35°	80	116
4-Bromo-2-methylpyridine 1-oxide			4-nitro-2-methylpyridine 1-oxide	48% HBr, urea, 160° or AcBr		67
4-Bromo-3-methylpyridine 1-oxide	72–73		4-nitro-3-methylpyridine 1-oxide	HBr, 140°, 4 hrs.		134
2-Bromo-4-nitropyridine 1-oxide	145–46		2-bromopyridine	peracetic acid, then HNO_3		24
3-Bromo-4-nitropyridine 1-oxide	152–53		3-bromopyridine 1-oxide	fum. HNO_3, H_2SO_4 90°.	40	21,39
4-Chloropyridine 1-oxide	152.5–53.5	147–48	4-nitropyridine 1-oxide	conc. HCl, sealed tube, 160°	80	23
	169.5		4-nitropyridine 1-oxide	acetyl chloride, 50°	90	18,57,147
			4-nitropyridine 1-oxide	$POCl_3$	57	16,44
	187–89		4-aminopyridine 1-oxide	Sandmeyer reaction	53	54
4-Chloromercuripyridine 1-oxide	259–60		pyridine 1-oxide	$Hg(OAc)_2$, HOAc, 130°, 2 hrs.	76	66
4-Chloro-2-methylpyridine 1-oxide			4-nitro-2-methylpyridine 1-oxide	conc. HCl, 160° or AcCl		67

(continued)

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides (*continued*)

Compound	M. p., °C	M. p., °C		Starting material	Conditions	Yield %	Ref.
		Hydrochloride	Picrate				
4-Chloro-3-methylpyridine 1-oxide	121			4-nitro-3-methylpyridine 1-oxide	acetyl chloride, 10 min.	70	134,77, 194
4-Chloro-2-methyl-3-nitropyridine 1-oxide	151			1-hydroxy-2-methyl-3-nitro-4(1*H*)-pyridone	$POCl_3$		64
4-Chloro-2-methyl-5-nitropyridine 1-oxide	154–55			1-hydroxy-2-methyl-5-nitro-4(1*H*)-pyridone	$POCl_3$		64
2-Chloro-3-methyl-4-nitropyridine 1-oxide	145–46			2-chloro-3-methylpyridine 1-oxide	H_2SO_4, fum. HNO_3, 4 hrs., 100°		138
2-Chloro-5-methyl-4-nitropyridine 1-oxide	154–55			2-chloro-5-methylpyridine 1-oxide	H_2SO_4, fum. HNO_3, 4 hrs., 100°		138
2-Chloro-6-methyl-4-nitropyridine 1-oxide	106–107			2-chloro-6-methylpyridine 1-oxide	H_2SO_4, fum. HNO_3, 4 hrs., 100°		138
4-Chloronicotinic acid 1-oxide	145–46			4-nitronicotinic acid 1-oxide	acetyl chloride 2.5 hrs. reflux	65	77
methyl ester	84						77

2-Chloro-4-nitropyridine 1-oxide	152–53		2-chloropyridine 1-oxide	H_2SO_4, fum. HNO_3, 4 hrs., 100°		138
4-Chloro-3-nitropyridine 1-oxide	147–49		1-hydroxy-3-nitro-4(1*H*)-pyridone	$POCl_3$		48
2,6-Diaminopyridine 1-oxide	206–07		2,6-diacetamidopyridine 1-oxide	10% NaOH, 100°, 8 hrs.	66	75
3,5-Dibromo-4-nitropyridine 1-oxide	198.5–99.5		3,5-dibromopyridine 1-oxide	H_2SO_4, fum. HNO_3, 90°, 1¼ hrs	90	28
3,5-Diethoxy-2-nitropyridine 1-oxide	164–65		3,5-diethoxypyridine 1-oxide	H_2SO_4, KNO_3, 0°, 1 day	90	28
4-Diethylaminopyridine 1-oxide		184–86	4-chloropyridine 1-oxide	Et_2NH, H_2O, sealed tube, 135°		16
2,6-Dimethyl-4-methoxypyridine 1-oxide	69–70		2,6-dimethyl-4-nitropyridine 1-oxide	reflux, $NaOCH_3$, $HOCH_3$, 1 hr.	90	122
2,6-Dimethyl-4-nitropyridine 1-oxide	163		2,6-dimethylpyridine 1-oxide			57
4,6-Dimethyl-2-nitropyridine 1-oxide	108–109		2-amino-4,6-dimethylpyridine 1-oxide	27% H_2O_2, 30% H_2SO_4 fum. 10–20°	40	138

(continued)

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides (*continued*)

Compound	M. p., °C.	M. p., °C. Hydrochloride	M. p., °C. Picrate	Starting material	Conditions	Yield %	Ref.
4-Ethoxypyridine 1-oxide[b]	33		125–26	4-nitropyridine 1-oxide			11,16
	126.5–27.5		126.5–27.5	4-nitropyridine 1-oxide	NaOH, EtOH, 3 hr. reflux	65	23
4-Ethoxy-2-methylpyridine 1-oxide				4-nitro-2-methylpyridine 1-oxide	$NaOC_2H_5$		53
2-Ethoxy-4-nitropyridine 1-oxide	132.5–33.5			2-ethoxypyridine 1-oxide	fum. HNO_3, H_2SO_4, 90°, 1¼ hr.	15[a]	24
Ethyl 6-benzyloxy-2-pyridinepyruvate 1-oxide	103–104			6-benzyloxy-2-methylpyridine 1-oxide	KOC_2H_5, ethyl oxalate	64	76
5-Ethyl-2-methylisonicotinic acid 1-oxide	194–94.5			5-ethyl-2-methylisonicotinonitrile 1-oxide	NaOH	96	115
5-Ethyl-2-methylisonicotinonitrile 1-oxide	107–108			4-amino-5-ethyl-2-methylpyridine 1-oxide	Sandmeyer reaction	43	115
5-Ethyl-2-methyl-4-nitropyridine 1-oxide	80			5-ethyl-2-methylpyridine 1-oxide	H_2SO_4, HNO_3 slowly to 100°	87	115,128

Ethyl 2-pyridine-pyruvate 1-oxide	72–73		2-picoline 1-oxide	KOC_2H_5, ethyl oxalate	35	76
Ethyl 4-pyridine-pyruvate 1-oxide	122–23		4-picoline 1-oxide	KOC_2H_5, ethyl oxalate	48	76
Ethyl nicotinate 1-oxide	99.5		nicotinic acid 1-oxide	esterification	50	35
2-(α-Hydroxyethyl) pyridine 1-oxide	97–99		2-pyridylethyl acetate	oxid'n, HCl hydrolysis	52[a]	72
Isonicotinonitrile 1-oxide	220–21		4-aminopyridine 1-oxide	Sandmeyer reaction	65	54
4-*i*–Propoxypyridine 1-oxide		124–5	4-nitropyridine 1-oxide	*i*-PrOH, nitrobenzene	92	45
4-Methoxynicotinic acid 1-oxide	202		4-nitronicotinic acid 1-oxide	$NaOCH_3$	60	77
methyl ester	141–43					77
amide	208–209					77
3-Methoxypyridine 1-oxide	101–102	159–60	3-pyridinol 1-oxide	diazomethane	67	146
4-Methoxypyridine 1-oxide	81.5–82.5	143–44	4-nitropyridine 1-oxide	H_3COH, 3 hrs.		11
		142–43	4-bromopyridine 1-oxide	reflux, $NaOCH_3$		66
4-Methoxy-2-methylpyridine 1-oxide	78		2-methyl-4-nitropyridine 1-oxide	$NaOCH_3$		67
2-Methoxy-4-nitropyridine 1-oxide	154.5–58.5		2-methoxypyridine 1-oxide	fum. HNO_3, H_2SO_4, 75°, 1.5 hrs.	55	95

(continued)

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides (*continued*)

Compound	M. p., °C.	M. p., °C. Hydrochloride	M. p., °C. Picrate	Starting material	Conditions	Yield, %	Ref.
3-Methoxy-4-nitropyridine 1-oxide	134–35			3-methoxypyridine 1-oxide	fum. HNO_3, H_2SO_4, 75°, 1.5 hrs.	70	95
4-Methoxy-3-nitropyridine 1-oxide	192–93			4-chloro-3-nitropyridine 1-oxide	$NaOCH_3$		48
Methyl nicotinate 1-oxide	97			nicotinic acid 1-oxide	esterification		35
2-Methyl-4-nitropyridine 1-oxide	156–56.5			2-picoline 1-oxide	fum. HNO_3, H_2SO_4, 80°, 2 hrs.	85	24,53,13
3-Methyl-2-nitropyridine 1-oxide	110–11			3-methyl-2-aminopyridine 1-oxide	as above	55	138
4-Methyl-2-nitropyridine 1-oxide	118–19			4-methyl-2-aminopyridine 1-oxide	as above	52	138
5-Methyl-2-nitropyridine 1-oxide	112–13			5-methyl-2-aminopyridine 1-oxide	as above	45	138
6-Methyl-2-nitropyridine 1-oxide	120–21			6-methyl-2-aminopyridine 1-oxide	as above	57	138

3-Methyl-4-nitropyridine 1-oxide	129–33 137.5			3-picoline 1-oxide	H_2SO_4, KNO_3, 14 hrs. at 100°	35[a]	91 134
2-Methyl-4-phenoxypyridine 1-oxide		161–62		4-nitro-2-methylpyridine 1-oxide	$NaOC_6H_5$		67
4-Morpholinopyridine 1-oxide	75–78			4-chloropyridine 1-oxide	morpholine, H_2O 5 hrs., sealed tube, 130°	53	16,57
4-Nitronicotinic acid 1-oxide	170–72			4-nitro-3-methylpyridine 1-oxide	H_2SO_4, $Na_2Cr_2O_7$, 30°	56	77
4-(*p*-Nitrophenylthio)-pyridine 1-oxide	154–55			4-chloropyridine 1-oxide	$NaSC_6H_4NO_2$-(*p*)		50
2-Nitropyridine 1-oxide	85–86			2-aminopyridine 1-oxide	27% H_2O_2, 30% fum. H_2SO_4, 10–20°	50	138
4-Nitropyridine 1-oxide	159		161–62	pyridine 1-oxide	mixed acids, 130°, 3.5 hrs.	72	57
				pyridine 1-oxide	fum. HNO_3, H_2SO_4 90°, 1.5 hrs.	90	23
4-Phenoxypyridine 1-oxide	130–31	166–67.5	138–39	4-nitropyridine 1-oxide	$NaOC_6H_5$		11
Picolinamide 1-oxide	161–62			picolinic acid 1-oxide	esterification, NH_4OH	80	58
Picolinic acid 1-oxide	162–63			ethyl 2-pyridinepyruvate	NaOH, H_2O_2, 80°, 10 hrs.	79	76

(continued)

TABLE IV-2. Pyridine 1-Oxides Prepared from Other Oxides (*continued*)

Compound	M. p., °C.	M. p., °C.		Starting material	Conditions	Yield, %	Ref.
		Hydrochloride	Picrate				
Isonicotinic acid 1-oxide	265–66			ethyl 4-pyridinepyruvate	NaOH, H_2O_2, 80°, 10 hrs.	68	76
2-Pyridineacetonitrile 1-oxide	134–35			ethyl α-oximino-2-pyridinepropionate 1-oxide	NaOH, heat	44	76
4-Pyridineacetonitrile 1-oxide	184–85			ethyl α-oximino-4-pyridinepropionate 1-oxide		49	76
2-Pyridinemethanol 1-oxide	143–43.5			2-pyridylmethyl acetate	oxid'n, HCl hydrolysis	60[a]	72
3-Pyridinesulfonic acid 1-oxide	237–38			pyridine 1-oxide	fum. H_2SO_4, 220–40°	51	123

[a] Yield for two steps, including oxidation.

[b] Different melting points suggest polymorphic modifications (*147*).

perature and may be followed by iodimetric titration of aliquots, indicating the consumption of the oxidizing agent. Several days may be required. The use of the easily prepared perphthalic acid was recommended by Bobranski (*3*). More recently the availability of peracetic acid and of 30% hydrogen peroxide and the success obtained with these oxidants in acetic acid has made them the agents of choice (*37*). Since the reaction may be quite vigorous, oxidation may require cooling initially, followed by heating to complete the reaction. Table IV-1 (pp. 99 ff.) presents data concerning the formation and properties of pyridine 1-oxides obtained by direct oxidation. The direct formation of oxides is limited in some circumstances such as the presence in the starting material of sterically hindering groups, *e.g.*, 2,6-diphenyl (*1,36*), 2,6-dibromo (*114*), 2,6-dialkoxy (*114*), or 2-nitro (*46*), particularly in conjunction with base-weakening substituents (77). 2,6-Dibromopyridine, a base which resisted oxide formation by the above reagents, was converted to the oxide in good yield by pertrifluoroacetic acid (*185*). In other cases, the problem is the presence of easily oxidizable substituents as sulfide (*32*), phosphine (*43*), aldehyde (*177*), hydrazide (*177*), or azo (*81*) linkages (although in the last-named case selective oxidation is sometimes possible (*81,158,160*)). Olefinic and azomethine double bonds were not attacked during oxide formation (*177*).

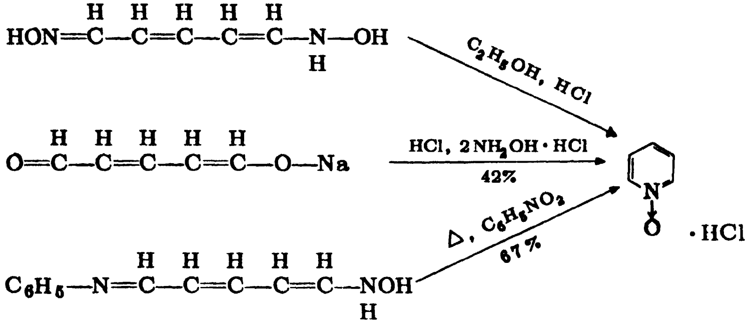
Degradation has been observed in the action of hydrogen peroxide in acetic acid on ethyl 2-pyridineacetate (*74*) and on certain bicyclic derivatives in which the nitrogen atom is at a bridgehead, such as quinolizones (*74*) and pyrrocolines (*78,80*). In each case picolinic acid 1-oxide or a derivative is obtained. Oxidation of aminopyridines to nitropyridines by hydrogen peroxide in the presence of strong acids has been reported (*85,86*). Hydrolysis of an amide group (*58*) and of a 2-chloro substituent (*74*) is sometimes caused by hydrogen peroxide in acetic acid. Many of these difficulties may be overcome by reactions performed on pyridines already bearing a 1-oxide grouping (Table IV-2, pp. 104 ff.).

2. From Other Oxides

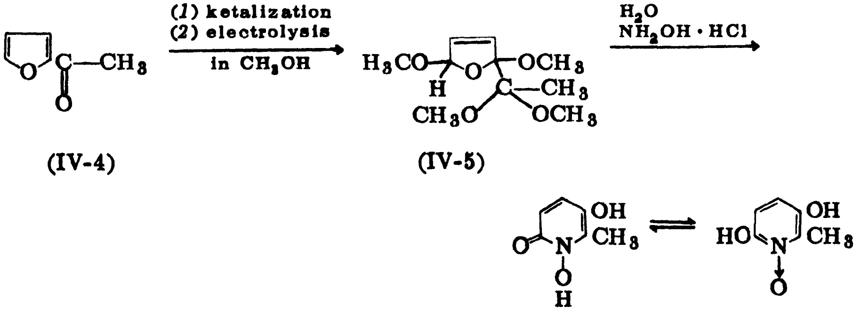
Many pyridine 1-oxides are readily accessible by substitution or displacement reactions on a pyridine oxide as a starting material. These reactions, which are discussed later (p. 121), are of particular synthetic importance for the preparation of substitution products not accessible by direct oxidation. The oxides so obtained are listed in Table IV-2 (pp. 104 ff.).

3. By Cyclization Reactions

Baumgarten and co-workers (*2*) observed that glutaconaldehyde dioxime was converted by alcoholic hydrochloric acid to pyridine oxide hydrochloride in fair yield (IV-3). The monoanil monooxime of the aldehyde was cyclized merely by heating. This approach has not been much extended. Recent developments in furan chemistry (*111–113*) have made accessible some polyfunctional aliphatic compounds whose reaction with hydroxylamine is similar to the above cyclizations. For example, 2-acetylfuran (IV-4), as the dimethyl ketal, on electrolysis in methanol provides a methoxylated dihydro derivative (IV-5, or tautomer). On treatment of an aqueous solution of the latter with hydroxylamine hydrochloride, an acidic substance soon precipitated which was considered to be the pyridine



(IV-3)

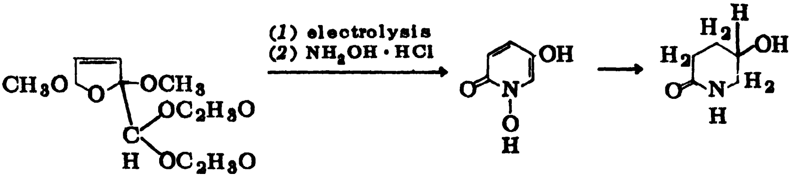


(IV-4)

(IV-5)

(IV-6)

oxide (IV-6 or tautomer). (*Cf.* p. 133.) It gave a deep violet color with ferric chloride, formed a mono- and diacetate, and lost one oxygen on reduction (*111*). In the related transformation (IV-7) the product was reduced with Raney nickel to the known 5-hydroxy-2-piperidone (*113*).

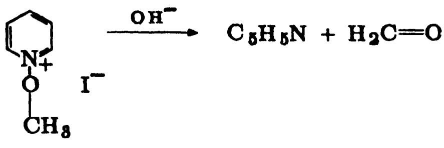


(IV-7)

B. PROPERTIES

Many pyridine oxides are solids (Tables IV-1 and IV-2, pp. 99 ff.), perhaps because of their increased polar character with reference to the parent pyridine. However, they retain considerable solubility in organic solvents as well as water, and some may be distilled at reduced pressure. Since the boiling points of the oxides often have a greater spread than those of the parent bases, improved fractionation as the oxides has been reported (*171*). In addition, analysis of mixtures of pyridines by paper chromatography of the oxides appears to be useful on a micro scale (*79*).

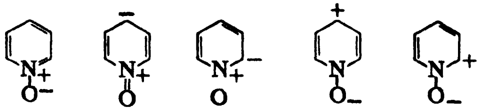
Like amine oxides in general, the pyridine 1-oxides retain some basic properties. The drop in basicity in passing from pyridine (pK = 5.29) to pyridine 1-oxide (pK = 0.79) is considerable. pK values have been obtained for a number of substituted pyridine oxides by potentiometric or spectrophotometric methods (*124*). Although weakly basic, many oxides form characteristic picrates and hydrochlorides that are often an aid in purification. In addition they react with alkyl halides at the oxygen atom. Thus the methiodide of pyridine 1-oxide is 1-methoxypyridinium iodide (IV-8) whose quaternary hydroxide decomposes readily to formaldehyde



(IV-8)

and pyridine (*15*). Interaction of pyridine oxide with trinitrobenzene has been detected in solution, but a solid complex could not be isolated (*150*).

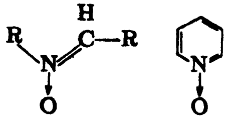
Linton (*5*) measured and compared the dipole moments of pyridine 1-oxide, trimethylamine oxide, and dimethylaniline oxide. Since the moment found for pyridine 1-oxide was considerably less than anticipated, he proposed that the final state of the molecule received contribution from structures IV-9 and IV-10 in which positions 2 and 4 are rich in electrons. It was pointed out by Ochiai that this conclusion implied an increased susceptibility of the ring in pyridine 1-oxide to substitution by electrophilic agents (*10,12,57*). The demonstrated ease of nitration mainly in the 4 position (*13*), in contrast to the great resistance of pyridine in this respect (Chapter I, p. 18), testified to the correctness of the interpretation. Subsequent contributions to the chemistry of pyridine oxides made by Ochiai and his collaborators in Japan (*57*) and independently by workers in a number of other laboratories (*21–34*) in the Western world suggested the importance of the additional resonance structures (IV-11, IV-12). (*Cf.* reviews *57,159,164*.)



(IV-9) (IV-10) (IV-11) (IV-12)

The various electronic structures pictured for pyridine oxide have now been supported by charge distribution calculations (*6,166*), by infrared studies showing the effect of electron release of the *N*-oxide group on the carbonyl stretching frequency of appropriate 4-substituents (*174*), and by measurements of the dipole moments of 4-substituted pyridine 1-oxides (*172*). In the work on dipole moments it was concluded that the pyridine oxide ring can create either a surfeit or deficit of electrons at the 4 position. (In contrast, the pyridine boron trichloride complex was judged capable of electron deficit only (*179*).)

An analogy between aldonitrones and pyridine 1-oxides (IV-13) had been drawn by Colonna (7), who noted similarities in the re-



(IV-13)

sponse of these classes of compounds to sulfuryl chloride and to Grignard reagents.

The ultraviolet absorption spectra of some pyridine 1-oxides are given in Table IV-3. For pyridine itself, conversion to the 1-oxide results in absorption at very nearly the same wavelength as the base but with much greater intensity. (The effect of solvents on the pyridine 1-oxide spectrum has been recorded (*188*).) With substituted pyridines, the presence of substituents, particularly in the 4 position, which can interact with the oxide function, result in a longer wavelength band for the oxide than the base (*180*), an effect that is nullified in the conjugate acids (*127,180*).

An absorption in the infrared region characteristic of the *N*-oxide bond in pyridine 1-oxide and in some of the picoline 1-oxides has

TABLE IV-3. Ultraviolet Absorption Spectra of Pyridine 1-Oxides

Compound	λ_{max} (mμ)	$\epsilon \times 10^{-3}$	Solvent	Ref.
Pyridine 1-oxide	213,265	16.7, 12.9	ethanol	73
	254	11.9	water	127
3-Picoline 1-oxide	209,254	19.8, 11.7	water	127
4-Picoline 1-oxide	212, 266	17.2, 14.7	ethanol	73
2-Aminopyridine 1-oxide	226, (248)[a], 319	21.0, 4.0, 5.0	ethanol	58
3-Aminopyridine 1-oxide	234, (252)[a], 314	22.8, 11.5, 2.7	water	127
4-Aminopyridine 1-oxide	276	19	water	127
2-Benzyloxypyridine 1-oxide	260, 305	8.6, 5.8	ethanol	30
2-Ethoxy-4-methylpyridine 1-oxide	261, 304	5.3, 3.0	ethanol	34
2-Ethoxy-6-methylpyridine 1-oxide	261, 299	3.6, 1.5	ethanol	34
Isonicotinic acid 1-oxide	216, 280	11.2, 17.1	water	127
Nicotinic acid 1-oxide	220, 260	22.4, 10.2	water	127
4-Nitropyridine 1-oxide	235, 330	10, 15.9	ethanol	25
2-Pyridinol 1-oxide (1-hydroxy-2-pyridone)	223, 303	7.2, 4.5	ethanol	30
3-Pyridinol 1-oxide	225, 263, 305	14.5, 10.4, 3.4	ethanol	30
4-Pyridinol 1-oxide	268	14.0	ethanol	30

[a] Inflection points

been noted at about 1266 cm.$^{-1}$ in carbon tetrachloride (*143*) and about 1270 cm.$^{-1}$ in carbon disulfide (*130,142*) (*cf.*, however, reference *146*). In the solid or liquid phase, a band at 1242 cm.$^{-1}$ has been found (*130*). In an extension of these studies to a sizable group of oxides of 2-substituted (*176*) and 4-substituted (*175*) pyridines in chloroform, a band, presumably N—O stretching, was generally found near 1242–1250 cm.$^{-1}$ unless shifted by substituents acting as electron acceptors. Possible adjacent subsidiary bands (1270–1300 cm.$^{-1}$) were noted.

C. REACTIONS

1. Reduction of the N—O Bond

The N—O bond in pyridine 1-oxide appears to be stronger than in aliphatic tertiary amine oxides such as trimethylamine oxide. The latter, in contrast to pyridine 1-oxide, readily oxidizes ferrous hydroxide suspensions (*4*). The resistance to reduction is also reflected in the lower reduction potential of pyridine oxide when compared to dimethylaniline oxide according to Ochiai (*10*). Resistance to certain reducing agents permits selective reduction of other substituents such as nitro (p. 131) or azoxy (*81*) without attack of the oxide linkage. For preparative purposes the reduction to pyridine bases is accomplished by methods described below.

Meisenheimer (*1*) observed the deoxygenation of pyridine 1-oxides by means of zinc and dilute acid. Den Hertog and his collaborators made use of iron in hot acetic acid and obtained good yields (*24*). Under these conditions, a nitro group is reduced to an amino group but a halogen can be retained (*23,83,116*). Ochiai (*57*) and Hamana (*56,63*) found that reduction to the parent base occurred in a number of cases when the oxide was treated with phosphorus trichloride in chloroform. While this method gave only a 48% yield of pyridine, a 79% yield of 4-nitropyridine was obtained from its 1-oxide. In the latter case, the use of phosphorus trichloride seems to be advantageous if retention of the nitro group is desired (*57*). 2-Nitropyridine 1-oxide (*138*) and the isomeric 4-nitropicoline 1-oxides (*120,91*) have similarly been reduced in good yield to the parent nitropyridines. Phosphorus tribromide also accomplished the reduction but with displacement of nitro by bromo (*128*). On the other hand, triphenyl phosphite did not affect 4-nitropyridine 1-oxide but did reduce pyridine oxide itself (*133*).

The removal of the *N*-oxide grouping by means of phosphorus trichloride is not a satisfactory procedure in the presence of substituents such as amino, but 4-acetamidopyridine 1-oxide and 4-pyridinol 1-oxide are successfully deoxygenated (*132,134*).

Hydrogenation in the presence of metal catalysts seemed for a while relatively little explored (*61,115*) as a means of deoxygenating pyridine oxides in contrast to the rather unusual reagents described above, but Katritzky and Monro showed that 5% palladized charcoal in ethanol was useful in a variety of cases (*178*). 2-Substituted pyridine 1-oxides reduced more slowly than the other isomers. Certain selective reductions were possible: side chain double bonds saturated before removal of 1-oxide function, for example. In other cases, the latter group was reduced first. Raney nickel in acetic anhydride also has recently proved effective as a hydrogenation catalyst for pyridine *N*-oxides at room temperature (*171*).

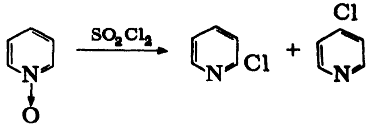
The alkaline decomposition of quaternary salts of pyridine oxides as discussed above (IV-8) has been investigated with some success both as a method of deoxygenation (*147,167*) and of synthesizing aldehydes (*167,169*).

Often the N—O bond is cleaved during reactions of pyridine oxides in which substitution of the ring or side chain is taking place, as described in the following section.

2. Substitution

a. Action of Halides of Sulfur or Phosphorus

Meisenheimer's observations on the formation of 4-chloroquinoline in a 73% yield by the action of sulfuryl chloride on quinoline oxide were probably the first realization of the effects of the *N*-oxide grouping in facilitating substitution reactions and influencing their orientation (*1*). Application of the method to pyridine 1-oxide by Bobranski *et al.* (*3*) led to a mixture of 2-chloropyridine (57%) and 4-chloropyridine (43%) (IV-14). The degree to which mixtures of



(IV-14)

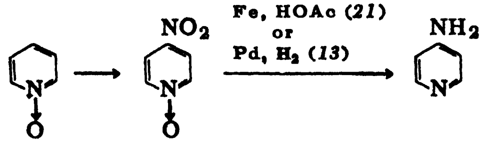
isomers are obtained depends largely on ring substituents, to judge from the limited number of examples reported. Thus, although 3-bromopyridine 1-oxide and sulfuryl chloride gave three isomeric monochloro derivatives (*22*), nicotinamide 1-oxide yielded only 2-chloronicotinonitrile (*74*) on treatment with phosphorus oxychloride and phosphorus pentachloride, providing a convenient route to certain 2,3-disubstituted pyridines (*cf.* also Chapter VI, p. 305).

Other examples of selective chlorination of the ring are known. For example, 2-picoline 1-oxide and phosphorus oxychloride yield 72% of 4-chloro-2-picoline (*121*). The similar conversion of a 3-substituted pyridine oxide to a single chloro derivative made an attractive new synthesis of ricinine possible (77) (IV-39). Removal of the *N*-oxide grouping is not a requisite for ring chlorination, since 3,5-diethoxypyridine oxide at reduced temperatures retained the oxide grouping while undergoing dichlorination (*181*).

A side reaction in the above type of chlorination may be the simultaneous displacement of a substituent such as methoxy (77) or nitro from the 4 position. Thus, 4-nitropyridine 1-oxide, when treated with sulfuryl chloride in a sealed tube at 110°, provides 2,4-dichloropyridine in yields near 40% (*21,27*). The displacement is characteristic for many substituents in the 4 position in pyridine oxides (*cf.* p. 128). Ring halogenation of an arylazo substituent has also been observed (*157*).

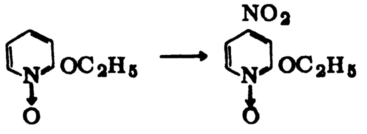
b. Nitration

Pyridine 1-oxide can be nitrated in fuming sulfuric acid with potassium nitrate or nitric acid at temperatures ranging from 100–130° (*13,46,60*) or by means of fuming nitric acid in sulfuric acid (*21,23*) at 90°. Yields may approach 90% of a mononitro derivative, m.p. 159°, which has been shown to be 4-nitropyridine 1-oxide (IV-15) by reduction to the known 4-aminopyridine (IV-16). A small amount of 2-nitration occurs (*46*). This result contrasts markedly



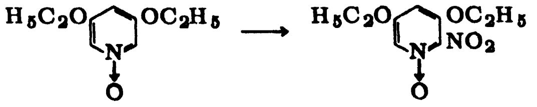
(IV-15) (IV-16)

with the difficulty in nitrating pyridine itself (*57*) which undergoes a slight conversion to a 3-nitro derivative above 300°. 4-Nitration appears to be characteristic of pyridine 1-oxides and has been observed for 2-picoline 1-oxide (*13,67*), 3-picoline 1-oxide (*91,134*), 2,6-lutidine 1-oxide (*57*), 3,5-dibromopyridine 1-oxide (*28*), and probably 3-bromopyridine 1-oxide (*39*). Nicotinonitrile 1-oxide underwent hydrolysis instead of nitration in the mixed acids (*39*). The directing influence of the 1-oxide grouping in electrophilic substitution exceeds that of an ethoxy group, since 2-ethoxy- and 3-ethoxypyridine 1-oxides both yield only a 4-nitro derivative (IV-17) (*24*).



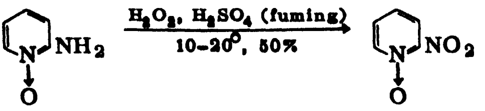
(IV-17)

However, the yield in the case of the 2-isomer was not high. Later, nitration in the 4 position was also observed with 2- and 3-methoxypyridine 1-oxides (*95*). Two ethoxy groups, however, took precedence over the 1-oxide grouping in directing nitration. Thus, 3,5-diethoxypyridine 1-oxide yielded a 2-nitro derivative in high yield (IV-18) (*28*). Similar orientation prevailed in the oxides of 3,5-dimethoxy- and 3-bromo-5-methoxypyridine (*116*). The reaction conditions had to be moderated to prevent deoxygenation and 2,6-dinitration (*28*). The possible effect of steric hindrance in determining the result was considered. In the interesting case of 2-phenylpyridine 1-oxide, nitration took place in the phenyl ring, mainly in the meta position (*173*).



(IV-18)

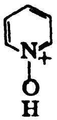
2-Nitropyridine 1-oxides, therefore, are not generally accessible by direct nitration. However, Brown (*138*) has prepared 2-nitropyridine 1-oxide and its homologs by oxidation of 2-aminopyridine 1-oxide (IV-19).



(IV-19)

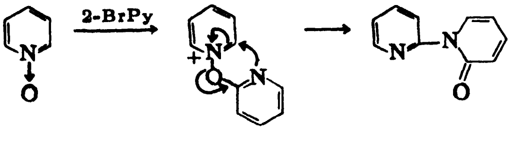
c. Other Substitution Reactions

While the nitration studies described, coupled with the easy displacement of the 4-nitro group in pyridine 1-oxides (*cf.* p. 128), already offer ample variety in the synthesis of 4-substituted pyridines, attempts to introduce substituents by a number of other electrophilic reagents familiar in aromatic chemistry have not been successful. Nitration in the 4 position of pyridine 1-oxides appears understandable in terms of contributions from reasonance structures such as IV-9. However, it is likely that most of the oxide actually exists in the protonated form (IV-20) in acid medium. This species would be expected to be similar to the pyridinium ion in resistance to electrophilic substitution. In consideration of this, Mosher and Welch have pointed out that sulfonation succeeded with pyridine oxide but that the conditions required were similar to those needed for pyridine itself, that is, fuming sulfuric acid at 220°. The product was a 3-sulfonic acid. Other attempts to obtain substitution, including bromination, chlorosulfonation, or Friedel-Crafts acylation, were unsuccessful (*123*). However, the mercuration of pyridine 1-oxide by treatment with mercuric acetate in glacial acetic acid at 130° has been reported to yield 76% of a 4-mercuri derivative (*66*) transformed with bromine to 4-bromopyridine 1-oxide Under the same conditions, another group found that mono- and dimercuration took place but that after bromination the products were 2-bromo- and 2,6 dibromopyridine oxide (*184*).



(IV-20)

Although it is profitable to attempt some clarification of the substitution reactions of pyridine oxides in terms of our knowledge of aromatic chemistry, other reactions resulting in substitution of the pyridine ring probably involve mechanisms more peculiar to the amine oxides. The oxygen atom is the initial site of attack of many reagents and its loss during the course of the reaction may signal its participation. These reactions possess no close analogy in purely benzenoid aromatic chemistry. For example, the reaction of pyridine 1-oxide with 2-bromopyridine, which leads to 1-(2-pyridyl)-2(1*H*)-pyridone (IV-22) (*62*), very likely proceeds by initial salt formation at the oxygen atom (IV-21) with a subsequent rearrangement



(IV-21) (IV-22)

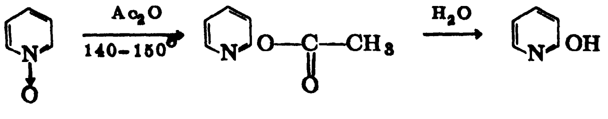
in which the joining of the rings is analogous to anionic attack on quaternary pyridinium compounds (Chapter III, p. 32). A similar product is formed from the oxide and 2-bromoquinoline. If the course of events is as pictured, the oxygen atom is transferred from one ring to the other. Further observations on the formation of 1-(2-pyridyl)-2(1*H*)-pyridones by interaction of pyridine oxides and 2-bromopyridine have been made (*154*).

The analogy between pyridine oxide and quaternary pyridinium salts in the probable importance of contributions from structures bearing positive charges at ring positions 2 or 4 is reflected in the ease of displacement of substituents in these positions by anions in both the oxides (p. 128) and quaternary salts (Chapter III, p. 32). However, pyridine oxide, in contrast to quaternary pyridinium salts, is not attacked by such nucleophilic agents as bisulfite or cyanide (*135*).

The formation of 2-phenylpyridine in low yield from the action of phenylmagnesium bromide on pyridine oxide was reported by Colonna (*7,155*) and subsequently confirmed (*47,135*).

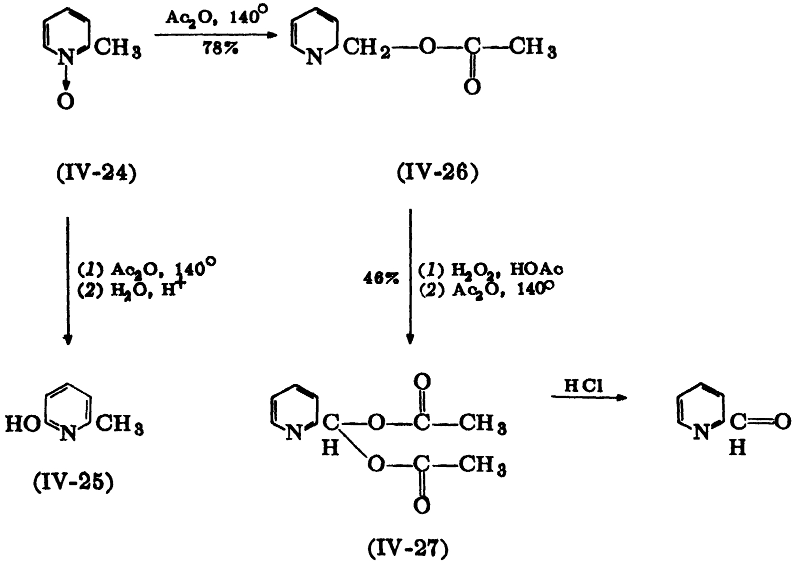
d. Action of Acetic Anhydride

Of considerable interest is the remarkable action of acetic anhydride on pyridine 1-oxide at 140°, which leads to 2-pyridinol (IV-23) in very high yield by way of the acetate (*40*). 3-Picoline 1-oxide



(IV-23)

by similar treatment was converted to 3-methyl-2-pyridinol (*72*). With alkyl groups in the 2 or 4 positions, however, the reaction may take a predominantly different course, resulting in side-chain oxidation. Thus, when 2-picoline 1-oxide (IV-24) is heated with acetic anhydride, some 6-methyl-2-pyridinol (IV-25) is formed, but the major product is 2-pyridinemethanol acetate (IV-26), which may be



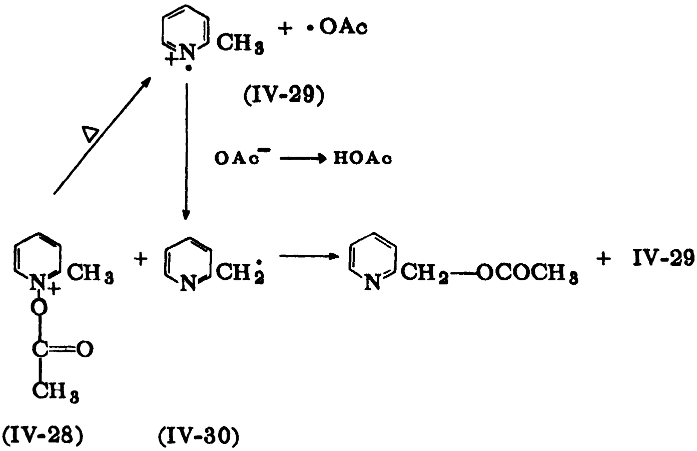
(IV-24)

(IV-26)

(IV-25)

(IV-27)

obtained in high yield (*72,73,119*). A number of 2-alkylpyridine 1-oxides were shown to undergo similar oxidation on the methylenic carbon adjacent to the ring. With 2,5- (*186*) or 2,4- (*149*) dialkyl substitution, attack is preferentially at the methylene adjacent to the 2 position unless other influences are operating; thus, 2,6-dimethyl-4-benzylpyridine 1-oxide with acetic anhydride leads to the phenyl pyridylcarbinol (*193*). Since 4-picoline 1-oxide is also converted to 4-pyridinemethanol acetate with acetic anhydride (*72,73*), a cyclic intermediate that would offer an attractive mechanism for oxidizing a 2-methyl group is inadequate. It has been proposed that a free radical mechanism is involved and that the N—O bond in the probable starting material (IV-28) undergoes homolytic cleavage to the radical IV-29, which is converted to 2-pyridylmethyl (IV-30). The reaction of the latter with starting material generates the product



and reforms radical IV-29 for a cyclic process. In support of a radical mechanism were the observations that the rate reaction when carried out in the presence of styrene induced its polymerization, and that the rate was very little affected by solvents of a wide range of polarity (*118*). The analogy of the proposed splitting of the N—O bond to that of peroxides was noted. However, although another study confirmed the presence of free radicals in the action of acetic anhydride on 2-picoline 1-oxide, the fact that added trapping agents removed these without influencing the yield of 2-pyridylmethyl acetate led the authors to doubt their importance in the rearrangement and to favor an intramolecular ionic mechanism (*165*).

The side-chain oxidation could be repeated with 2-pyridinemethyl acetate (IV-26) whose oxide led to the aldehyde diacetate (IV-27). This offers a useful route to picolinaldehyde (*72*) and certain 3-substituted derivatives (*152*). However, isonicotinaldehyde diacetate could be thus obtained only in poor yield; with 6-methyl-2-pyridinemethyl acetate, the 1-oxide gave 2,6-diacetoxypyridine and no aldehyde diacetate (*72*).

The formation of pyridylmethanols by the action of acetic anhydride on a pyridine oxide has been extended to the synthesis of pyridylalkanediols (*136,168*) and phenylpyridylcarbinols (*137,194*).

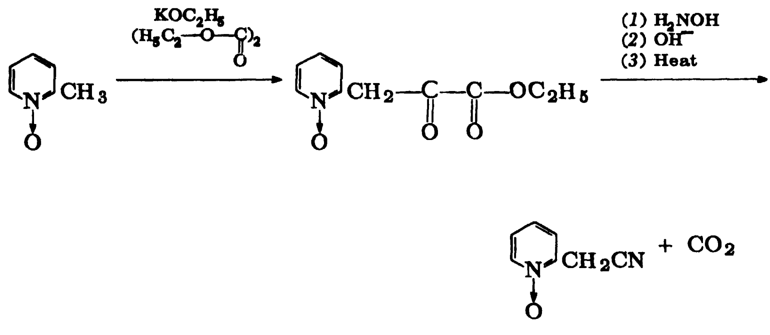
An isomeric 3-pyridinol is occasionally isolated in low yields from rearrangements of the above type in addition to the main product (*38,94,156*).

Substitution in the 3 position has been reported to occur when the adduct of *p*-toluenesulfonyl chloride and pyridine oxide is heated to about 205° (*97*). 3-Pyridinol was identified after hydrolysis of the intermediate *p*-toluensulfonate. At lower temperatures, the reaction is said to lead to the 2-isomer (*98*). Similar experiments have been carried out on picoline oxides (*71,99*). In another laboratory, it was found that 1-(2-pyridyl)-2(1*H*)-pyridones were among the reaction products when pyridine oxide and *p*-toluenesulfonyl chloride were heated (*145*). The reaction seems difficult to control and has little preparative value at present (*182*).

3. Reactions of Substituents

a. Side Chain Activation

The side chains in 2-picoline 1-oxide and 4-picoline 1-oxide may be condensed with ethyl oxalate in the presence of potassium ethoxide in yields of 35 and 48%, respectively, in contrast to the lack of reactivity of the picolines themselves. Saponification of the oxime of the resultant ester, followed by sublimation, provided 2-pyridineacetonitrile 1-oxide (IV-31) (*76*). The 4-isomer behaved similarly.

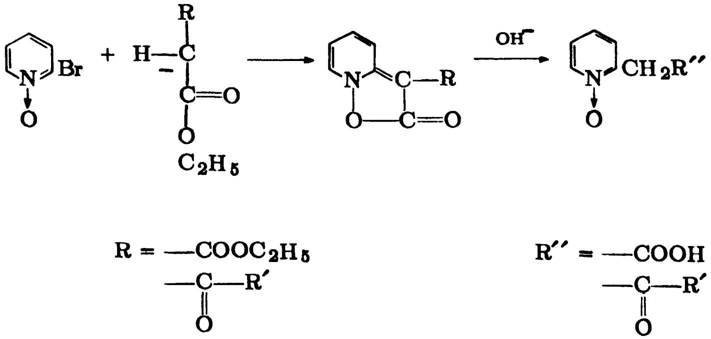


(IV-31)

b. Displacement of Nitro or Halogen Groups

A familiar feature of pyridine chemistry is the displacement of halogens in the 2 and 4 positions by a variety of anions and other nucleophilic agents. Although comparative rate studies have not been reported with the pyridine 1-oxides, such reactions are apparently more readily carried out. For example, in 2-bromopyridine 1-oxide, the bromine is readily replaced by OH^- or SH^- at water bath temperatures (*32*), whereas 2-halopyridines require more elevated temperatures (*81*). Displacements to form nitriles (*52*), thiocyanates (*151*), azides (*187*), or ethers and thioethers (*32,49,50*) are readily achieved with 2- or 4-halopyridine oxides. However, reaction with sodium or silver cyanate was not obtained (*187*).

2-Bromopyridine 1-oxide and its 6-methyl derivative react with the active methylene in the sodium salts of malonic ester or β-keto esters, but not of β-diketones. The product is not the oxide expected by simple displacement but, rather, a cyclic product derived from it by loss of alcohol, namely, an isoxazolono[2,3-a]pyridine. Compounds of this type were hydrolyzed by alkali with decarboxylation, yielding 2-pyridineacetic acid 1-oxide or related ketones (IV-32). Ethyl cyanoacetate underwent condensation with 6-bromo-2-picoline 1-oxide, but two products were isolated since cyclization occurred either at the cyano group or at the ester group (*153*).

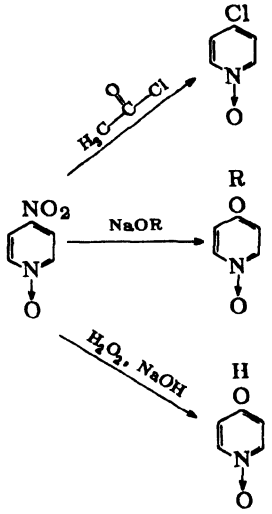


(IV-32)

An analogous cyclization has been reported to occur when the 1-oxide of 2-carbethoxyamidopyridine was heated at 140-50°; loss of ethanol accompanied formation of a pyridino-oxadiazolone (*141*), independently prepared from 2-aminopyridine 1-oxide and phosgene (*187*).

The reactions of the nitro group in 4-nitropyridine 1-oxide and its homologs have been studied in some detail by Ochiai and den Hertog and their collaborators. A number of unusual transformations have been reported. The importance of these reactions lies in the accessibility of 4-nitropyridine 1-oxides by nitration. After effecting the desired changes, one may remove the oxygen at the ring nitrogen. A new method is thus available for the preparation of substituted pyridines. The heightened activity of 4-nitro- and 4-halopyridine oxides to displacement by nucleophilic agents is similar to that found in the quaternary salts of the parent bases (Chapter III, p. 22) undoubtedly for the same reason, that is, contributions from resonance structures such as IV-11 and IV-12 in which the positive charge of the nitrogen atom may be localized in the 2 or 4 positions.

4-Nitropyridine 1-oxide can readily be converted to the 4-chloro or 4-bromo oxide with acetyl chloride or bromide (*57*) (IV-33). 2-

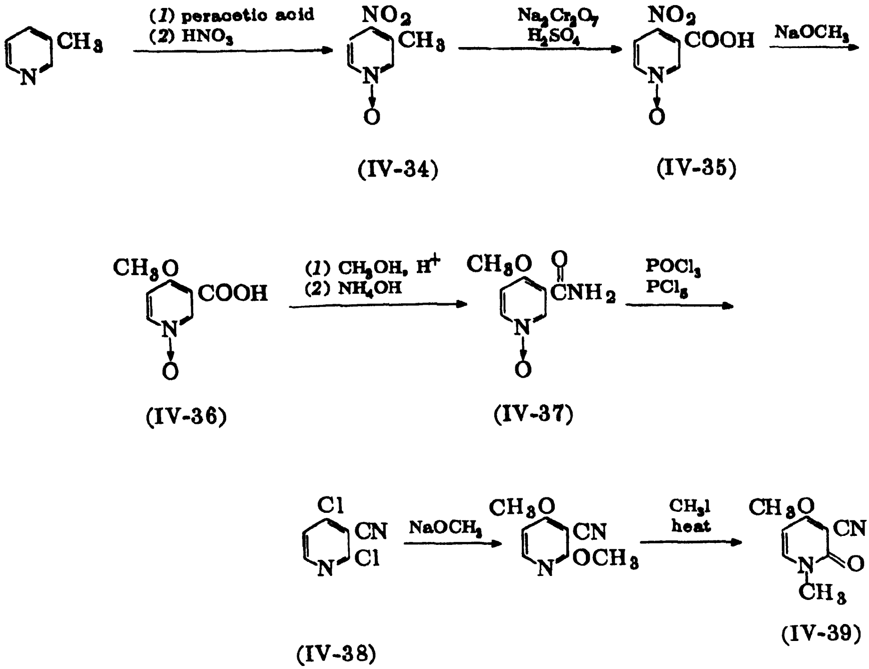


(IV-33)

Nitropyridine 1-oxides behave similarly (*138*). Thus, treatment of 4-nitropyridine 1-oxide with acetyl chloride at the boiling point results in a 90% yield of 4-chloropyridine 1-oxide (*18,57*), also produced by the action of hydrochloric acid under reflux (*23*) or phosphorus oxychloride at 70° (*18*). (At higher temperatures, 2,4-dichloropyridine results (*27*)). Depending on conditions, the action of hydrogen bromide in acetic acid or water produced 4-bromopyridine oxide and by-products resulting from hydrolysis or bromination (*23,55*). Replacement of the nitro group by OH can be accomplished in yields of about 60% by heating with sodium hydroxide and hydrogen peroxide at 50° (*25*) or by the action of acetic anhydride near 100° (*51*). In the latter case, dimethylaniline was added to absorb the nitrite formed and prevent side reactions. 4-Nitropyridine 1-oxide is said to be more stable to the action of water alone than is 4-nitropyridine, which hydrolyzes at 60° (*25*). However, ether formation was reported in refluxing alcohols and phenols; nitrobenzene served well as a solvent (*45*). Ether formation with alcoholates (*11,23*), phenolates (*11*), and thiophenolates (*16*) was generally readily achieved. Displacement of the nitro group of 4-nitropyridine 1-oxide by ammonia or primary or secondary amines has not proceeded in satisfactory yields (*16,82*). In some cases, 4,4′-azopyridine 1,1′-dioxide was the main product (*11*). Compounds such as 4-morpholinopyridine 1-oxide were better prepared from 4-chloropyridine 1-oxide than from the nitro compound. Many of these reactions have been carried out as well on homologs of pyridine. They are summarized in Table IV-2 (pp. 104 ff.), which includes pyridine oxides obtained from other oxides by substitution and displacement reactions. The importance of these chemical changes lies in the possible utilization of the simple pyridine bases as starting materials for more complex derivatives in a new manner. A synthesis of the alkaloid ricinine (IV-39) from β-picoline by Taylor and Crovetti (*77*) demonstrates the usefulness of pyridine oxide chemistry. 3-Picoline 1-oxide yields a 4-nitro derivative (IV-34), which was oxidized to 4-nitronicotinic acid 1-oxide (IV-35). The nitro group was displaced by methoxide to yield 4-methoxynicotinic acid 1-oxide (IV-36), the amide of which (IV-37) was formed by conventional methods. When this was treated with phosphorus pentachloride, ring chlorination in the 2 position occurred without formation of the 6-isomer. In the same step, the amide was dehydrated and the 4-methoxy group displaced by chloride. The resulting 2,4-dichloronicotinonitrile (IV-38) was converted to ricinine (IV-39) by known procedures.

Reactions of 4-nitropyridine 1-oxides are summarized in Chapter VIII, Tables VIII-2 (pp. 497 ff.) and VIII-11 (pp. 543 ff.).

In addition to the displacement reactions of 4-nitropyridine 1-oxides, other properties are worth noting. Catalytic reduction with palladium in neutral solution or dilute hydrochloric acid provides 4-aminopyridine 1-oxide (*57*), but reduction in acetic acid containing acetic anhydride proceeds further in some cases to the amino-

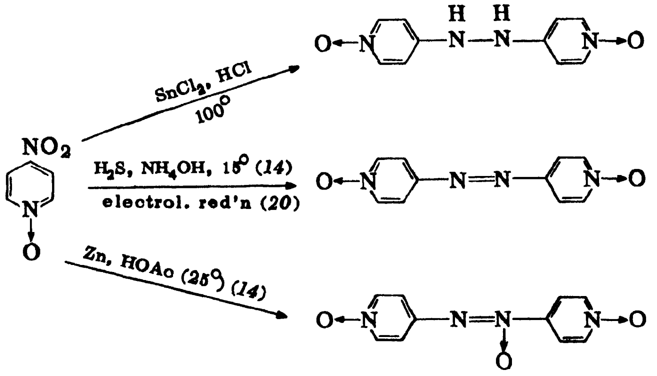


(IV-34) (IV-35)

(IV-36) (IV-37)

(IV-38) (IV-39)

pyridine or aminopicoline (*41,91,134*). Complete reduction of 4-nitropyridine 1-oxide to 4-aminopyridine has also been achieved with hydrosulfite (*14*) or Raney nickel catalyst (*68*), and the nitro compounds thus provide a useful route to 4-aminopyridines. However, a variety of chemical reducing agents lead to bimolecular reduction products (IV-40) (*57,26*). Similar behavior was shown by



(IV-40)

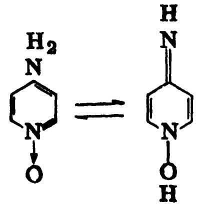
4-nitro-2-picoline 1-oxide (*41*). The reduction of the *N*-oxide linkage proceeds subsequent to the reduction of the nitro group (*26*). The ultraviolet spectra of many of the bimolecular reduction products have been recorded (*26*).

Reduction reactions of 4-nitropyridine 1-oxides are summarized in Chapter VIII, Tables VIII-10 (pp. 542 f.) and VIII-14 (pp. 517 f.).

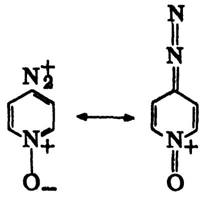
D. AMINOPYRIDINE 1-OXIDES

The aminopyridine 1-oxides have not been prepared by direct oxidation of aminopyridines, since the amino group itself is susceptible to oxidation. For example, treatment of 2-aminopyridine with hydrogen peroxide leads to 2-nitropyridine (*85,86*). However, 2-dibenzamido- (*93*) and 2-acetamidopyridine (*75*) on oxidation and hydrolysis readily provide 2-aminopyridine 1-oxide. The Hofmann degradation of 2-picolinamide 1-oxide is an alternate route (*58*). 4-Aminopyridine 1-oxides have generally been prepared by catalytic reduction (palladium) of the nitro compounds in neutral solution (*57*), since these are readily available by direct nitration of pyridine 1-oxides. 2-Aminopyridine 1-oxide gives a deep blue color with ferric chloride (*58*).

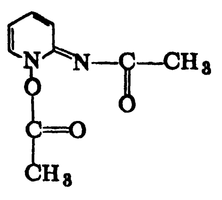
The properties of the aminopyridine 1-oxides are, in part, those of arylamines of low basicity due to an electronegative ring substituent. In addition, special properties due to tautomeric and resonance possibilities are manifested, judging from the limited information at hand. Thus, both 2-amino- (*93*) and 4-aminopyridine 1-oxide diazotize readily and undergo coupling reactions. The 4-diazonium salt has been converted by the Sandmeyer reaction to the nitrile (*54*) or to halo derivatives (*57*). The greater stability of the diazonium compounds of the 2- and 4-aminopyridine oxides over those of aminopyridines may be due to resonance interaction with the oxide grouping (IV-43) (*115*). The formation of diacyl derivatives (*54*) reflects a tautomerism (IV-41, IV-42). For example, with the 2-isomer, acetylation led to a diacetyl derivative considered, on the basis of infrared studies, to be IV-44 rather than 2-diacetamidopyridine 1-oxide (*75*). Such a tautomeric relationship has been shown to exist between 1-hydroxy-2(1*H*)-pyridone and 2-pyridinol 1-oxide (p. 134). In contrast to the hydroxy series was the absence of reac-



(IV-41) (IV-42)



(IV-43)



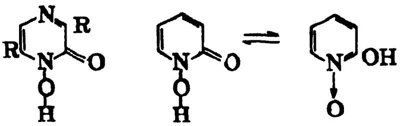
(IV-44)

tion with diazomethane (*54*). However, Katritzky has concluded that 2-aminopyridine 1-oxide exists in solution mainly in the amino and not the imino form on the basis of a comparison of its ultraviolet spectrum (*162,163*) and basicity (*163*) with those of alkylated tautomeric forms. The same conclusion was reached for the 4-amino isomer (*163*).

In 3-aminopyridine and its oxide, most of the considerations of tautomerism and resonance interactions pertinent to the 2- and 4-isomers do not apply. The reduction in basicity in passing from 3-aminopyridine (pK = 6.09) to the 1-oxide (pK = 1.47) (*124*) probably accounts for the failure of the latter to condense with acetoacetic ester or acetylacetone (*131*) in contrast to 3-aminopyridine itself. On the other hand, the condensation product of ethoxymethylenemalonic ester and 3-aminopyridine 1-oxide apparently cyclized at the 4 position, whereas the corresponding 3-aminopyridine derivative cyclized at the 2 position (*131*). In this instance, the *N*-oxide link determined the orientation in a manner reminiscent of nitrations.

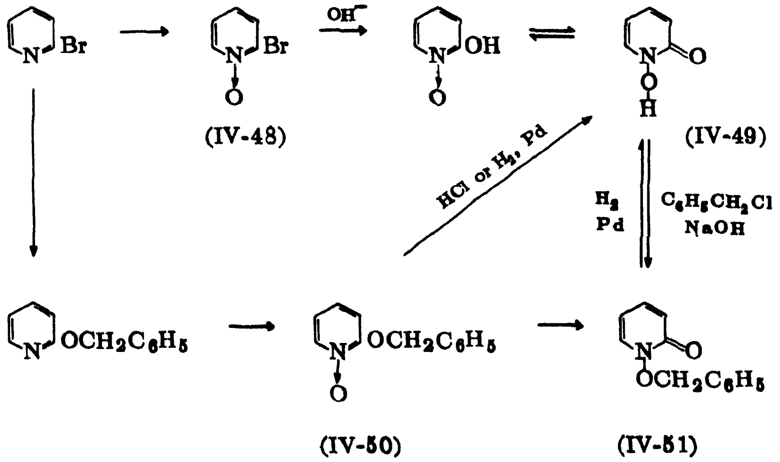
E. PYRIDINOL 1-OXIDES (*N*-HYDROXYPYRIDONES)

The discovery by Dutcher and Wintersteiner (*29*) that the antibiotic aspergillic acid has a 1-hydroxy-2-pyrazinone (IV-45) structure drew attention to the cyclic hydroxamic acid grouping not previously encountered among natural products. In the hope of devising general methods for introducing such structures into heterocyclic systems and of obtaining antibacterial agents, work was undertaken in the pyridine series by Shaw *et al* (*30–32*). It was felt that a synthesis directed towards the 2-pyridinol 1-oxide (IV-47) would lead to the 1-hydroxy-2(1*H*)-pyridone (IV-46) in view of a



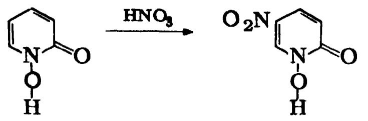
(IV-45) (IV-46) (IV-47)

postulated tautomerism. The desired acid was readily obtained by either of two methods starting with 2-bromopyridine. The 1-oxide (IV-48) was prepared and observed to undergo ready alkaline hydrolysis to an acidic substance, m.p. 149–150°, which gave a deep red color with ferric chloride and formed a copper salt. Alternatively, 2-benzyloxypyridine was converted to an *N*-oxide (IV-50) which was debenzylated by means of hydrogen and palladium or hot hydrochloric acid to yield the same acid (IV-49). Treatment of the sodium salt of the acid with benzyl chloride yielded a benzyl ether isomeric with IV-50 and therefore considered to be the pyridone (IV-51). The ultraviolet spectra of the isomeric benzyl ethers (IV-50, IV-51) were quite different from each other, but the spectrum of

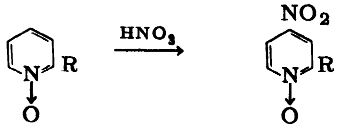


the single acid obtained from them agreed clearly with the pyridone isomer. Thus the tautomeric relationship was demonstrated, but the pyridone formula represents the stable tautomer. (The acid was prepared independently by Newbold and Spring (*33*).) Isomerization of the oxide (IV-50) to the pyridone (IV-51) was also observed (*30*).

Chemical evidence also supports the representation of the 2-pyridinol 1-oxides as 2-pyridones, since nitration proceeds readily to the 5-nitro derivative (*31,95*) or a 3,5-dinitro derivative (*144*), characteristic orientation of 2-pyridones (IV-52). In contrast, the 1-oxide grouping generally directs nitration into the 4 position (IV-53) even in the presence of groups with powerful orienting ability such as ethoxy (*24*), methoxy (*95*), and acetamido (*92*). Direct oxidation of 2-pyridone to 1-hydroxy-2(1*H*)-pyridone by means of perbenzoic acid has been achieved in low yields (IV-54) (*30*).

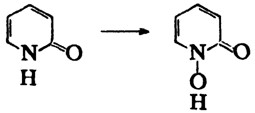


(IV-52)



(IV-53)

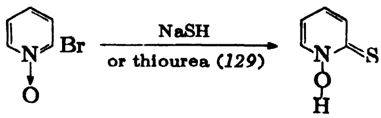
R = —OCH_3, —OC_2H_5, —$NHCOCH_3$



(IV-54)

The cyclic pyridine hydroxamic acids proved to have considerable antibacterial activity as hoped, often exceeding that of the antibiotic, aspergillic acid (*31,139*).

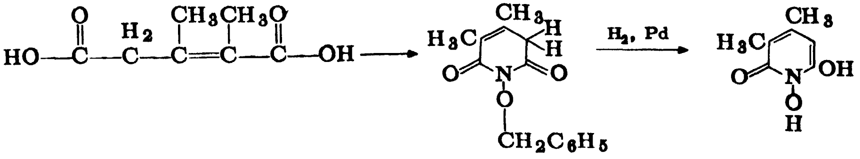
An interesting variation in the structure of these acids is the introduction of sulfur as in 1-hydroxy-2(1*H*)-pyridinethione, obtained readily from 2-bromopyridine 1-oxide (IV-55), which is the parent member of a series of particularly potent antibacterial agents (*32*)



(IV-55)

and powerful chelating agents. Their preparation and properties are summarized in Table IV-5 (p. 141).

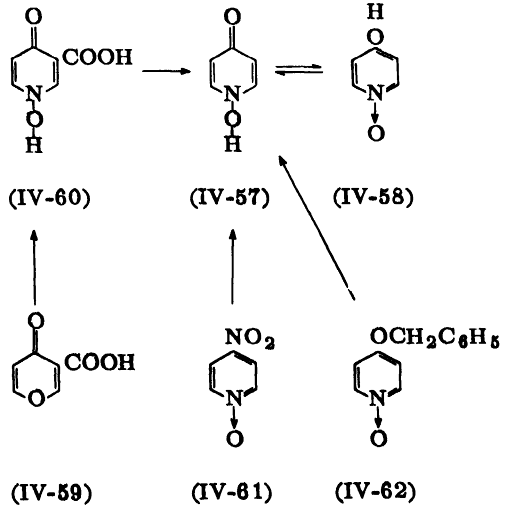
A synthesis of 1-hydroxy-2(1*H*)-pyridones by a cyclization reaction utilized a glutaconic acid and *o*-benzylhydroxylamine (IV-56) (*114*).



(IV-56)

The preparations of 1-hydroxy-2(1*H*)-pyridone and its substituted derivatives are summarized in Table IV-4 (pp. 138 ff.).

3-Pyridinol 1-oxide and the 4-isomer have also been prepared. As in the case of the 2-isomer (*30,34*), independent syntheses of 4-pyridinol 1-oxide or 1-hydroxy-4(1*H*)-pyridone have been reported in recent years (*30,51,57,59*) by workers investigating the chemistry of pyridine oxides. However, Ost (*87*) and Peratoner (*88*) studied the reactions of γ-pyrones with hydroxylamine much earlier, and provided a route to the 1-hydroxy-4(1*H*)-pyridones (IV-57). Coumalic acid (IV-59), for example, yielded the nicotinic acid derivative IV-60, which was decarboxylated (*87*).



(IV-60) (IV-57) (IV-58)

(IV-59) (IV-61) (IV-62)

TABLE IV-4. 1-Hydroxypyridones

Compound	M. p., °C.	Starting material	Conditions	Yield, %	Ref.
1-Hydroxy-2(1*H*)-pyridone	149–50	2-benzyloxypyridine 1-oxide	H_2, Pd, ethanol	69	30
		2-benzyloxypyridine 1-oxide	reflux 20% HCl, 10 min.	68	30
		2-ethoxypyridine 1-oxide	3*N* HCl, 100°, 2 hrs.		33
		2-bromopyridine 1-oxide	10% NaOH, 100°, 1.5 hrs.	53	32
		2(1*H*)-pyridone	perbenzoic acid, room temp., 1 week	15	31
1-Hydroxy-3-bromo-2(1*H*)-pyridone	208–9	1-hydroxy-2(1*H*)-pyridone	Br_2, HOAc, room temp.,	13	31
1-Hydroxy-5-bromo-2(1*H*)-pyridone	137–39	2-benzyloxy-5-bromopyridine 1-oxide	20% HCl, reflux, 10 min.	13	31
		5-bromo-2(1*H*)-pyridone	perbenzoic acid, room temp., 1 week	18	31
1-Hydroxy-6-bromo-2(1*H*)-pyridone	155–57	6-bromo-2(1*H*)-pyridone	perbenzoic acid, room temp., 1 week	19	31
1-Hydroxy-3-methyl-2(1*H*)-pyridone	138–39	2-ethoxy-3-methylpyridine 1-oxide	3*N* HCl, 100°, 3 hrs.	...	34
1-Hydroxy-4-methyl-2(1*H*)-pyridone	131–33	2-ethoxy-4-methylpyridine 1-oxide	3*N* HCl, 100°, 3 hrs.	15	34
	129–30	2-benzyloxy-4-methylpyridine 1-oxide	HCl	75	31
1-Hydroxy-6-methyl-2(1*H*)-pyridone	141–42	6-benzyloxy-2-methylpyridine 1-oxide	H_2, Pd, ethanol	72	76
		6-benzyloxy-2-methylpyridine 1-oxide	15% HCl, reflux, 30 min.	59	76

1-Hydroxy-3-chloro-4(1*H*)-pyridone	258–59	4-nitropyridine 1-oxide	6% HCl, 180°, 3 hrs.	20	25
1-Hydroxy-3,5-dibromo-2(1*H*)-pyridone	186–88	1-hydroxy-2(1*H*)-pyridone	Br_2, H_2O	35–40	144
1-Hydroxy-3,5-dibromo-4(1*H*)-pyridone	ca. 240 (dec.)	1-hydroxy-4(1*H*)-pyridone	Br_2		25,65
1-Hydroxy-3,5-diiodo-4(1*H*)-pyridone	335–38	1-hydroxy-4(1*H*)-pyridone	ICl, HCl, H_2O, 100°, 1 hr.		65
1-Hydroxy-3,5-dinitro-2(1*H*)-pyridone	194	1-hydroxy-2(1*H*)-pyridone	fum. HNO_3, HOAc, 40°	80–85	144
1-Hydroxy-3,5-dinitro-4(1*H*)-pyridone	201–3 (dec.)	1-hydroxy-4(1*H*)-pyridone	HNO_3, HOAc, 100°	80	48
		1-hydroxy-3-nitro-4(1*H*)-pyridone	HNO_3, HOAc, 100°		48
1-Hydroxy-3,5-dinitro-2-methyl-4(1*H*)-pyridone	215–17	1-hydroxy-4(1*H*)-pyridone	HNO_3, HOAc, 70°	67	64
1-Hydroxy-3-iodo-4(1*H*)-pyridone	304–307	1-hydroxy-4(1*H*)-pyridone	HCl, ICl		65
1-Hydroxy-2-methyl-4(1*H*)-pyridone	192–93	2-methyl-4-benzyl-oxypyridine 1-oxide	H_2, Pd		67
1-Hydroxy-3-methyl-4(1*H*)-pyridone	224	4-acetoxy-3-methyl-pyridine 1-oxide	dil. HCl		134
1-Hydroxy-2-methyl-3-nitro-4(1*H*)-pyridone	224–25	1-hydroxy-2-methyl-4(1*H*)-pyridone	HNO_3, HOAc, 70°	44	64
1-Hydroxy-2-methyl-5-nitro-4(1*H*)-pyridone	221	1-hydroxy-2-methyl-4(1*H*)-pyridone	HNO_3, HOAc, 70°	15	64
1-Hydroxy-3-nitro-4(1*H*)-pyridone	219–21	1-hydroxy-4(1*H*)-pyridone	HNO_3, Ac_2O, 75°	90	48

(continued)

TABLE IV-4. 1-Hydroxypyridones (*continued*)

Compound	M. p., °C.	Starting material	Conditions	Yield, %	Ref.
	225–26	4-nitropyridine 1-oxide	Ac_2O, 100°	30–50	98,83
1-Hydroxy-5-nitro-2(1*H*)-pyridone	198–99	1-hydroxy-2(1*H*)-pyridone	HNO_3 in HOAc, room temp. or 0°	67	31,95
1-Hydroxy-(X,Y)-dinitro-2(1*H*)-pyridone	193.5–94.5	1-hydroxy-2(1*H*)-pyridone	Fuming HNO_3, HOAc	60	95
1-Hydroxy-4(1*H*)-pyridone	243–44	4-benzyloxypyridine 1-oxide	H_2, Pd, ethanol	68	30,57
		4-nitropyridine 1-oxide	NaOH, H_2O_2, 50°	60	25
		4-nitropyridine 1-oxide	Ac_2O, dimethylaniline, 100°	63	51,57
		4-chloropyridine 1-oxide	20% KOH, 5 hrs. reflux		25
		4-methoxypyridine 1-oxide	acetyl chloride		59

TABLE IV-5. 1-Hydroxypyridinethiones

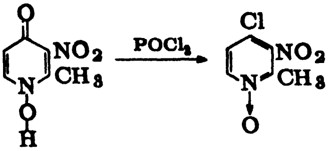
Compound	M. p., °C.	Starting material	Conditions	Yield, %	Ref.
1-Hydroxy-2(1*H*)-pyridinethione	68–70	2-bromopyridine 1-oxide	aq. NaHS, 100°	61	32
			thiourea, hydrolysis	56	32
1-Hydroxy-5-bromo-2(1*H*)-pyridinethione	130–31	2,5-dibromopyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	40	32
1-Hydroxy-3-ethoxy-2(1*H*)-pyridinethione	101–103	2-bromo-5-ethoxy-pyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	85	32
1-Hydroxy-3-methyl-2(1*H*)-pyridinethione	74–75	2-bromo-3-methyl-pyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	52	32
1-Hydroxy-4-methyl-2(1*H*)-pyridinethione	59–61	2-bromo-4-methyl-pyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	60	32
1-Hydroxy-5-methyl-2(1*H*)-pyridinethione	106–107	2-bromo-5-methyl-pyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	53	32
1-Hydroxy-6-methyl-2(1*H*)-pyridinethione	52–54	2-bromo-6-methylpyridine 1-oxide	aq. NaHS, 100°, 1.5 hrs.	50	32
1-Hydroxy-4(1*H*)-pyridinethione	140	4-chloropyridine 1-oxide	thiourea, hydrolysis	72	49,57

Recent syntheses include the hydrolysis of 4-nitropyridine 1-oxide (IV-61) (*25,51,57*), 4-chloropyridine 1-oxide (*25*), 4-methoxypyridine 1-oxide (*25*), and hydrogenolysis of 4-benzyloxypyridine 1-oxide (*30*). (Side reactions may occur in the displacement of the nitro or chloro group, leading to a 3-nitro (*51*) or 3-chloro (*25*) derivative of the product.)

A benzyl ether of each tautomeric form (IV-57 and IV-58) was obtained, but ultraviolet spectroscopic evidence was inconclusive in determining which tautomeric structure best represents the single crystalline acid, m.p. 243–244°, obtained by all synthetic approaches. (Infrared methods have not been applied.) Following a demonstration that the Hammett equation is applicable to the basicities of pyridine 1-oxides (*124*), Jaffé estimated the pK for the equilibrium of one tautomeric form and its conjugate acid. Comparison with the observed value led him to favor the 4-pyridinol 1-oxide structure (*125*), a choice supported also by molecular orbital calculations of the relative stabilities of the tautomeric structures (*126*). However, such calculations for the 1-hydroxy-2(1*H*)-pyridone pair favored the oxide structure, which is excluded by spectroscopic evidence (*30*). In this chapter, the acid and its derivatives are considered as 4-pyridones analogous to the 1-hydroxy-2(1*H*)-pyridones and are so listed in Table IV-4 (*cf*. reference *163*).

Tautomeric behavior is encountered in the reactions of 1-hydroxy-4(1*H*)-pyridone. Ochiai and Hayashi (*59*) report the formation of both 1-methoxy-4(1*H*)-pyridone and 4-methoxypyridine 1-oxide on treatment of the acid with diazomethane (cf. also *183*). In substitution reactions, orientation characteristic of 4-pyridone is found—that is, formation of 3- and 3,5-substituted derivatives—rather than the orientation characteristic of pyridine 1-oxides. 4-Acetamidopyridine 1-oxide, for example, yields a 2-nitro derivative (*92*). 1-Hydroxy-4(1*H*)-pyridone forms 3-nitro- and 3,5-dinitro-1-hydroxy-4(1*H*)-pyridone (*48,70*) on nitration in glacial acetic acid. The structures were proved by conversion to aminopyridines. Bromination (*25,65,70*) and iodination (*65*) follow a similar course.

The reaction of certain 1-hydroxy-4-pyridones with $POCl_3$ is of interest since chloro derivatives of the tautomeric 4-pyridinol 1-oxide are formed. Thus, 1-hydroxy-2-methyl-3-nitro-4(1*H*)-pyridone leads (*64*) to a 4-chloro 1-oxide (IV-63). Likewise, 3-chloro-1-hydroxy-



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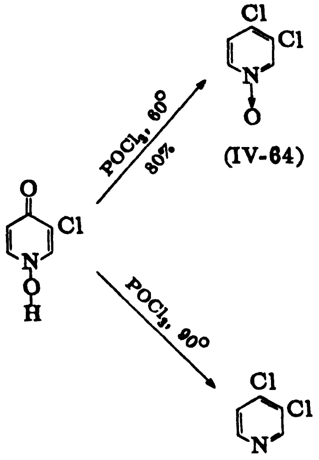


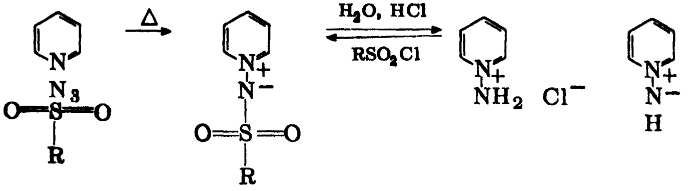
(IV-64)

4(1*H*)-pyridone yields 3,4-dichloropyridine 1-oxide (IV-64) at 60° but 3,4-dichloropyridine itself at 90° (*83*). Phosphorus trichloride reduces 1-hydroxy-4(1*H*)-pyridone to 4(1*H*)-pyridone (*56*), in the manner characteristic of many pyridine 1-oxides. Sulfuryl chloride in this case leads to a highly chlorinated product, C_5Cl_7NO (*83*); the ring is too susceptible to halogenation to permit selective introduction of one chloro atom.

The chemistry of the 1-hydroxy-4-pyridone nucleus derives added interest from the recent discovery (*96*) of a natural product of the quinoline series which incorporates such a grouping.

F. 1-AMINOPYRIDINIUM SALTS AND PYRIDINE ARYLIMINES

Related to pyridine 1-oxides is the small but interesting group of nitrogen analogs, derived from the 1-aminopyridinium ion (IV-65), which have been characterized in the form of crystalline salts, acyl, or sulfonyl derivatives. The free base (IV-66) has not been isolated, decomposing readily into ammonia and pyridine.



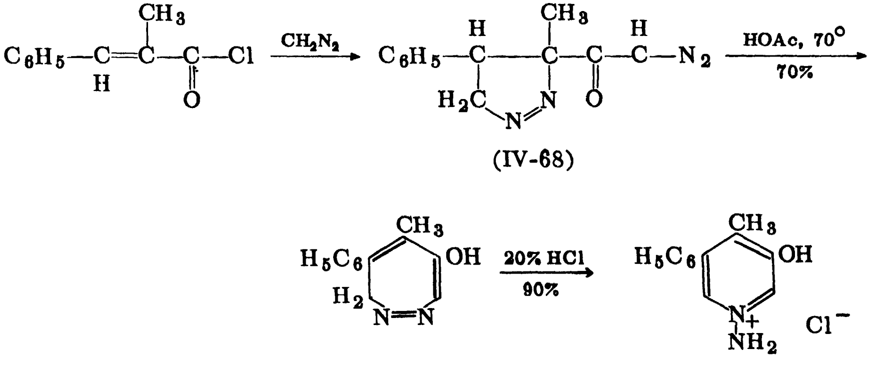
(IV-67) (IV-65) (IV-66)

The preparation of the 1-aminopyridinium ion and the clarification of its structure were achieved by Ashley, Buchanan, and Easson (*102*) in a reinvestigation of earlier work of Curtius on the reactions of sulfonyl azides. The latter had been observed to effect nuclear substitution of the aromatic ring with formation of *N*-arylsulfonamides. Therefore, the product obtained from heating pyridine with sulfonazides was considered to be probably a 2-sulfonylamidopyridine (*101*). When later workers attempted to apply the reaction to the preparation of sulfapyridine, using *p*-acetamidobenzenesulfonyl azide, the products obtained raised doubts about the earlier interpretation. Datta (*103*) and Ashley *et al.* (*102*) concluded that the azide had reacted at the ring nitrogen to yield the dipolar sulfonamide (IV-67). The insolubility of the product in alkali is in contrast to the solubility of the isomeric 2-, 3-, or 4-sulfonylamidopyridines. The formulation as a 1-substituted pyridine gains support from the properties of the hydrolysis product described below. The condensation of sulfonyl azides with pyridine is achieved by prolonged refluxing (2–3 days) and may be followed by measurement of the evolved nitrogen. Benzene- and 2-naphthalenesulfonazide studied by Curtius (*101*) take the same course (*104*). Yields are moderate.

Hydrolysis of the sulfonamide link in compounds such as IV-67 is achieved only by severe acid conditions. That 1-aminopyridinium chloride (IV-65) can be crystallized from the reaction mixture testifies to its stability in acid. The chloride (m.p. 160°) or picrate is different from derivatives of the known aminopyridine isomers (*102*). Treatment with nitrous acid gave pyridine. Catalytic hydrogenation over platinum oxide yielded ammonia, pyridine, and piperidine unless acetic anhydride was present, in which case the acetyl derivative of the known 1-aminopiperidine could be isolated.

The 1-aminopyridinium ion can be acetylated or treated with benzenesulfonyl chlorides (*102,104*), permitting reconstitution of the original sulfonamides (IV-67).

An unusual approach to 1-aminopyridinium derivatives involving contraction of a seven-membered ring has been described by Moore (*110*). The pyrazoline (IV-68) obtained by treatment of α-methylcinnamoyl chloride with diazomethane rearranged, when heated, to a red substance considered to be 4-hydroxy-5-methyl-6-phenyl-7*H*-1,2-diazepine (IV-69). When the latter was heated in aqueous acid, the hydrochloride of the 1-aminopyridine (IV-70) was obtained in high yield.

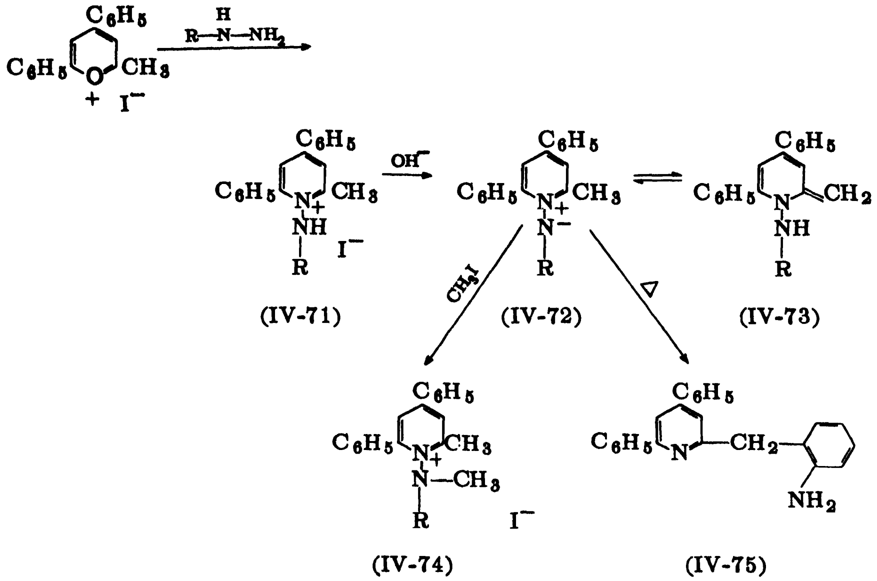


(IV-68)

(IV-69)

(IV-70)

As is often the case in pyridine chemistry, compounds of the above type may be obtained from heterocycles with a ring oxygen atom. *N*-Aryl derivatives of the 1-aminopyridinium ion have been prepared by Schneider and his colleagues by treatment of pyrylium salts with substituted hydrazines in benzene solution (IV-71) (*105–108*). (*Cf.* Chapter II, pp. 211 ff., and Table II-30, pp. 223 ff.)

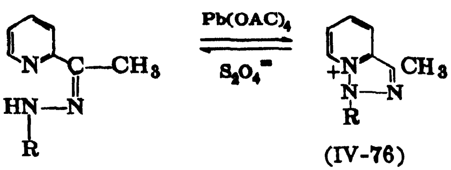


(IV-71) (IV-72) (IV-73)

(IV-74) (IV-75)

In some cases, an intermediate hydrazone was obtained which could be cyclized in acetic acid as a separate step (*108*). In accordance with the structure given was the ready cleavage by catalytic reduction or by zinc in alkali to the substituted pyridine and R—NH_2 (*106*). When R was phenyl in IV-71, treatment of the quaternary iodide with alkali produced a deep blue anhydro base, best represented as the pyridylimine (IV-72) (*105*). Although the presence of tautomeric anhydro base (IV-73) was indicated by characteristic reactions with carbon disulfide and phenyl isocyanate (*cf.* p. 39), a deep blue anhydro base could be obtained in other structural modifications of IV-71 that did not permit methide formation. Further evidence for the dipolar structure (IV-72) was the formation of the *N*-methyl derivative (IV-74) on treatment with methyl iodide (*105*). As mentioned above, 1-aminopyridine is stable only in acid. The formation of more or less stable anhydro bases such as IV-72 is possible when R is aryl, permitting resonance stabilization of the anionic charge in a manner reminiscent of the pyridinium ylides (Chapter III, p. 43). (*Cf.* review *161.*)

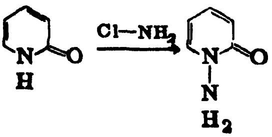
An interesting property of the pyridine arylimines (IV-72) is the rearrangement that occurs in hot alcohol leading on an *o*-aminobenzylpyridine (IV-75) (*106,107*). Dimroth and his colleagues have studied the effect of solvent and structure on the spectral properties of the arylimines and also on their thermal rearrangement (*189*).



(IV-76)

Formation of a bicyclic derivative of 1-aminopyridine (IV-76) has been achieved by an intramolecular oxidation of a hydrazone of 2-acetylpyridine (*109*).

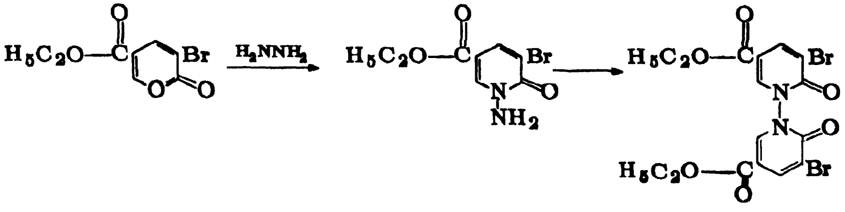
1-Amino-2(1*H*)-pyridone (IV-77a) has been obtained by direct introduction of an amino group into 2-pyridone through the action



(IV-77a)

of chloramine on the sodium salt (*190*). Yields of about 35% were obtained from 2-pyridone and its isomeric ring methyl derivatives. The products were weakly basic, deaminated to the parent pyridone on treatment with nitrous acid, and could be acylated (*191*). 1-Amino-2(1*H*)-pyridone formed a bicyclic derivative on treatment with phosgene (*192*).

Pyridones derived from 1-aminopyridine have been prepared from 2-pyrones by the action of hydrazine (*100,140*) or phenylhydrazine (*140*). For example, bromocoumalic ester (IV-77), when treated



(IV-77) (IV-78) (IV-79)

briefly with hydrazine near 0° permitted the isolation of the 1-aminopyridone (IV-78). Without precautions of time or of temperature, the 1,1'-dipyridone (IV-79) was obtained. The amino compound (IV-78) was basic, reacted with benzaldehyde, and could be reduced to the parent pyridone (*100*).

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CHAPTER V

Alkylpyridines and Arylpyridines

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A. ALKYL- AND ARALKYLPYRIDINES

1. Preparation

In Chapter II (Part One, pp. 99 ff.) the synthesis of pyridine derivatives from starting materials lacking the pyridine nucleus has been surveyed; obviously, many of these general syntheses are suited to the preparation of the compounds of the present chapter. The synthetic methods discussed herein, on the other hand, are limited to those in which the starting material is itself a pyridine derivative.

a. Pyrolysis and Degradation of Natural Products

The isolation of pyridine and many of its homologs from coal, various coal relatives, and petroleum sources has been discussed in Chapter II (pp. 113 ff.).

Many natural products, especially among the large class of alkaloids, are structurally related to pyridine (*1*). Such substances yield pyridine derivatives on pyrolysis in the presence or absence of alkali. Frequent use is made of zinc dust or selenium to remove oxygen or dehydrogenate an initially formed piperidine ring. Alkylpyridinecarboxylic acids which may be formed are usually decarboxylated during the pyrolysis (*176*). The method is of little value in preparative work but is very useful in the elucidation of structures of natural products. The application of these methods is found in the listed degradation studies (*1–25*).

Representative alkylpyridines obtained from such pyrolytic reactions are listed with their natural sources in Table V-1 (p. 158); see also Chapter II, Table II-10 (pp. 140 ff.).

b. Reduction Methods

Alkylpyridines are often obtainable by reducing a group attached either to the pyridine nucleus or to a side chain.

The commonest reducible functions are halo, hydroxy, carbonyl, and olefin. This method is very useful since the starting materials are often readily prepared.

(a) Halogen Compounds. The use of zinc (*26*) or zinc and hydrochloric acid (*27*) to prepare 2,6-lutidine from its 4-chloro (*26*) or 4-bromo (*27*) derivative was reported in the early literature of pyridine chemistry. Hydriodic acid was also used in the early work,

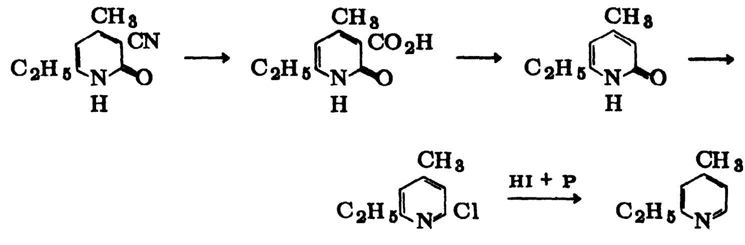
TABLE V-1. Alkylpyridines Obtained in the Pyrolysis of Natural Products

Alkyl derivative	Source	Ref.
2-Methyl	anabasine	2
3-Methyl	nicotine	3
3-Methyl	strychnine	4
3-Methyl	cinchonine	5
3-Methyl	brucine	6
4-Methyl	spartein	7
2-Ethyl	anabasine	2
3-Ethyl	nicotine	3
3-Ethyl	cinchonine	8
3-Ethyl	brucine	9
4-Ethyl	brucine	9
2-Propyl	coniine	10
2-Propyl	cytisine	11
2-Ethyl-4-methyl	solanum pseudocapsicum	12
2-Ethyl-5-methyl	cevine	13,14
2-Ethyl-5-methyl	jervine	15
2-Ethyl-5-methyl	solanidine	16
2-Ethyl-5-methyl	tomatidine	17
3-Ethyl-4-methyl	cinchonine	18
3-Ethyl-4-methyl	meroquinene	19
5-Ethyl-2-methyl	solanum pseudocapsicum	12
3-Butyl	fusarinic acid	20
3,4-Diethyl	coryantheine	21
2,4-Dimethyl-3-ethyl	aspidospermine	22
3-Ethyl-4-*i*-propyl	coryantheine	23
3,5-Dimethyl-2-propyl	cytisine	11,24
3-Amyl-5-methyl	cytisine	25

and the results of Ost (*28*) in the hydriodic acid reduction of 4,5-dichloro-2-trichloromethylpyridine and 4,5,6-trichloro-2-trichloromethylpyridine to 5-chloro-2-picoline showed that halogen in the 2 and 4 positions on the ring and in the 2 position on the side chain is more readily removed than in the 3 position on the ring.

A mixture of phosphorus and hydriodic acid was used by Ruzicka and Fournasir (*29*) to reduce 2,6-dichloro-3-ethyl-4-picoline to 3-ethyl-4-picoline and by Bardhan (*30*) to obtain 2-ethyl-4-picoline from 2-chloro-6-ethyl-4-picoline. Bardhan also used zinc as a reducing agent. Yields were not given so a comparison cannot be made. His method for the preparation of 2-ethyl-4-picoline (V-1) is a good illustration of the steps involved in the syntheses of alkylpyridines, making use of reduction in the last step.

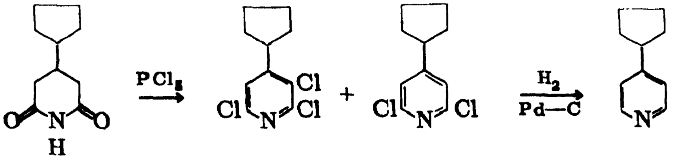
$CH_3CH_2COCH_2COCH_3 + NCCH_2CONH_2 \longrightarrow$



(V-1)

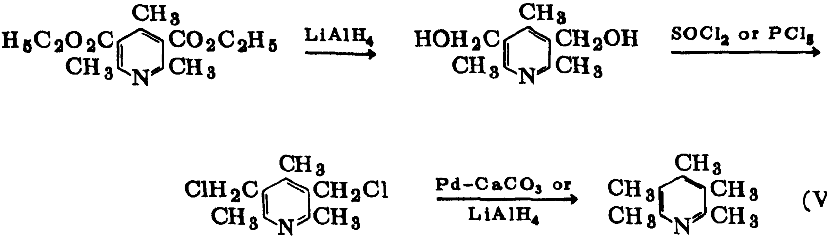
A series of 2-benzylpyridines has been prepared by Sperber *et al.* (*31*) by the conversion of the phenylpyridylcarbinol with thionyl chloride to the corresponding chloride, then reducing with zinc and acetic acid. Over-all yields ranged from 45 to 82%. A similar method was employed by Leonard and Ryder (*32*) to prepare 2-*n*-butyl-3-picoline and 6-*n*-butyl-3-picoline. Yields were 78 and 73%, respectively. Bis(2-pyridyl)methane was prepared by a similar reduction of bis(2-pyridyl)chloromethane (*33*).

Catalytic reduction over palladium catalyst, either by itself or on a carrier such as charcoal or barium carbonate, has been used for both nuclear and side-chain halogen. The nuclear chlorines were preferentially removed from 3-(β-chloroethyl)-2,6-dichloro-4-picoline to give 3-(β-chloroethyl)-4-picoline (*480*). In connection with the chemistry of pyridoxine, Harris (*34*) reduced 4,5-bis(bromomethyl)-2-methyl-3-pyridinol to 2,4,5-trimethyl-3-pyridinol with palladium on barium carbonate in 40% yield. Using a reaction similar to Bardhan's (*30*), Tracy and Elderfield (*35*) prepared 2,3-lutidine by catalytic reduction. Similar reactions were employed by Woodburn and Hellman (*36*) in the preparation of 3-*n*-propyl- and 3-*n*-butyl-2-picolines, by Prelog and his group for cycloalkeno-2,3-pyridines (*323–325*), and by Tsuda's group for 2,3,5-, 2,3,6-, 2,4,5- and 3,4,5-collidines (*332,333*). 2-Cyclopropylpyridine was obtained by Mariella *et al.* (*37*) following a similar series of reactions. The reduction was run in basic solution, since the cyclopropyl ring was reduced under acidic conditions. Additional applications of this reduction may be found in the synthesis of 3,4-lutidine (*38*), 3,5-lutidine (*432,789*), 3-ethyl-2-picoline (*38*), 2-*i*-butylpyridine (*39*), 2-*n*-butyl-3-picoline (*40*), 6-*n*-heptyl-2-picoline (*41*), and 4-cyclopentylpyridine (V-2) (*42*). Pentamethylpyridine was prepared by Karrer and Mai-



(V-2)

noni starting with the classical Hantzsch synthesis (V-3). Lithium aluminum hydride was also used to reduce the chloro groups, but the authors prefer the catalytic method (*43*).



(V-3)

(b) Hydroxy Compounds. The reducing agents for halogen have also been used in the reduction of hydroxyl groups. The yields are not good and the method is not used to any great extent; it is generally preferable to convert the hydroxyl first to halogen and then reduce.

The following reducing agents have been used: zinc in the conversion of 2,6-dimethyl-4-pyridinol to 2,6-lutidine (*44*); hydriodic acid to obtain 3,4-diethylpyridine from 3-ethyl-4-pyridineethanol (*45,46*) and diphenyl(2-pyridyl)methane (*243*) and phenyl-(2-pyridyl)-(2-thienyl)methane (*47*) from the carbinols; phosphorus and hydriodic acid to reduce α-ethyl-α-methyl-4-pyridinemethanol to 4-*s*-butylpyridine (*180*); and hydrogen over Adams catalyst to reduce the 4-hydroxymethyl group in pyridoxine to a methyl group (*34*). It is interesting in this last connection that the 3-hydroxymethyl group was not reduced; an ethyl ether of the 4 group was also reduced. 3-Ethyl-4-(α,α′-dihydroxyisopropyl)pyridine has been converted to the di-*p*-toluenesulfonic ester and then reduced with lithium aluminum hydride to 3-ethyl-4-*i*-propylpyridine (*23*).

(c) Carboxylic Acids. There is very little in the literature on the reduction of carboxylic acids to alkyl groups. Šorm (*48*) has obtained 2- and 4-picolines by the zinc–acetic acid reduction of the corresponding acids. Wibaut and Boer obtained 30–35% yield of 2- and 4-picolines by the electrolytic reduction of picolinic and isonicotinic acids (*242*).

(d) Carbonyl Compounds. The reduction of a carbonyl group in the side chain by means of either the Clemmensen method (*49*) or the Wolff-Kishner method and its modifications (*50*) has proved very useful for the preparation of alkylpyridines.

The first instance of the application of the Wolff-Kishner method in pyridine chemistry was the preparation of 3-ethyl-4-picoline from 3-acetyl-4-picoline (*51*). Since then numerous applications of this reaction have been reported. These include the preparation of 3-ethyl-2-picoline (*52*), 3-ethyl-2,6-lutidine (*52*), 3-ethylpyridine (*3,53, 177*), 2-ethylpyridine (*54,55*), 3,4-diethylpyridine (*56*), 3-*n*-butylpyridine (*57*), 3-*n*-amylpyridine (*58*), 2-(3-methylamyl)pyridine (*178*), 2-*p*-(β-dimethylaminoethyl)benzylpyridine (*59*), 5-*n*-butyl-2-picoline (*20*), and 5-*n*-hexyl-2-picoline (*20*).

The Huang-Minlon modification (*60*) of the Wolff-Kishner reaction was adopted by Fand and Lutomski (*53*) for the preparation of 3-ethylpyridine in 80% yield. A comparison of the Huang-Minlon modification with the original Wolff-Kishner method for the preparation of 2-ethylpyridine gave crude yields of 65 and 50%, respectively (*55*).

The hydrazone method gave a higher yield, 72%, as against 48% for the semicarbazone method in the preparation of 5-*n*-butyl-2-picoline (*20*). Increasing chain length of the alkyl group of the ketone apparently does not lower the yields, as indicated in the preparation of 3-amylpyridine from 3-valerylpyridine (*58*) and 5-*n*-hexyl-2-picoline from 5-hexanoyl-2-picoline (*20*).

An interesting application of the Wolff-Kishner reduction is the conversion of the hydrazone of 2-pyridone to pyridine in 75% yield using copper sulfate or ferric chloride as a catalyst (*61*). No application of this reaction to the preparation of alkylpyridines is reported, although lepidine was obtained from 2-lepidone by this method (*62*). The application of the Wolff-Kishner reduction to diketones, *e.g.*, nicotinoylacetone, resulted in cleavage and the formation of 3-ethylpyridine (*57*).

Both the Huang-Minlon and Wolff-Kishner methods have been used in the preparation of 1-(2-pyridyl)-2-(aryl or heteroaryl)-ethane and the corresponding 3-pyridyl compound where the aryl group was phenyl (*63,64*) and the heteroaryl was 2-furyl (*63*) or 2-thienyl (*63*).

The Clemmensen reduction has not been applied as often as the Wolff-Kishner. Keto esters and keto acids have been reduced to give the pyridyl alkyl esters and acids (*24,65*), a 91% yield of 3,5-dimethyl-2-pyridinebutyric acid being obtained from 3,5-dimethyl-2-succinoylpyridine (*24*). However, the reduction of 3,5-dimethyl-2-propionylpyridine by the same method gave a very low yield of 3,5-dimethyl-2-propylpyridine, most of the product being the hydroxyl compound (*24*). 4-Benzylpyridine was obtained by LaForge from the 4-benzoyl derivative (*66*).

2-Ethylpyridine was obtained in 80% yield by Furst (*55*) using the Clemmensen reduction; however, Holland and Nayler (*67*) were unable to confirm his results. Like Späth and Galinovsky (*24*), they obtained the hydroxyl compound instead.

Other reducing agents have been used to reduce keto groups. A catalytic method, based on Rosenmund and Karg (*68*), was used to obtain 6-propyl-2-picoline from 6-acetonyl-2-picoline (*69*). The reaction is run in glacial acetic acid using a palladium catalyst and perchloric acid as an activator. In the absence of perchloric acid, hydrogenation is incomplete. Other catalytic methods tend to reduce the ring (*70,71*). 3-Benzylpyridine was obtained by phosphorus–hydriodic acid reduction of 3-benzoylpyridine (*244*).

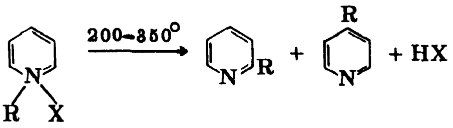
(e) Olefinic Compounds. The reduction of an alkene group to an alkane is not widely used as a preparative method. The pyridylalkenes are not always readily obtained, and the reactions of metallopyridines with halogen compounds give better results in the preparation of alkylpyridines.

2-Stilbazole has been reduced with hydriodic acid to 2-phenethylpyridine (*72*). When stronger reducing agents are used the pyridine ring is also hydrogenated (*73*). 2-Ethylpyridine was prepared by hydrogenation of 2-vinylpyridine over Raney nickel at room temperature (*74*), and 2-*n*-amylpyridine by the reduction of 2-(3-pentenyl)pyridine (*179*). 1,2-Bis(2-pyridyl)ethylene was hydrogenated over platinum to give a 90% yield of the ethane derivative (*33*), and the corresponding 4-pyridyl compound over palladium (*75*). 1,2-Bis(4-pyridyl)ethane has also been obtained by the action of sulfur on 4-picoline (*76*). 2- and 4-Picolines are benzylated to phenethylpyridines by benzyl alcohol in the presence of potassium hydroxide. The reaction probably involves the formation of a stilbazole, and its subsequent reduction by the benzyl alcohol (*691*).

c. Ladenburg Rearrangement

This reaction, the thermal rearrangement of an alkyl- or benzylpyridinium halide to an alkyl- or benzylpyridine (V-4), is historically important as the first instance of the preparation of alkylpyridines from pyridine (*77*).

As shown in equation V-4, a mixture of the 2- and 4-isomers is usually obtained. The 2,4-disubstituted derivative is also formed



(V-4)

R = alkyl, benzyl
X = halo

(*78,79*). The formation of the 3-isomer in the preparation of 2-ethylpyridine has also been reported (*80*) although in very small amount. By-products such as ethane and ethylbenzene are also formed (*78,79,81*). In the preparation of 2-propylpyridine the alkyl group isomerized to give 2-*i*-propylpyridine (*78*).

The reaction can also be applied to pyridine homologs (*82*), and was used by Chichibabin to prepare benzylpyridines (*83,84*).

By using a copper catalyst, Chichibabin and Rjumschin (*80*) shortened the heating time in the preparation of 2-ethylpyridine. The catalyst has been used more extensively in the preparation of 2- and 4-benzylpyridines and their homologs (*67,80,85–90*).

The separation of the isomeric products poses a problem. The difficulty in separating the alkyl isomers, which is discussed further in the section dealing with their properties (pp. 174 ff.), has limited the application of this reaction in the synthesis of alkylpyridines.

The isomeric benzylpyridines have been separated by various methods. Following Chichibabin (*80,83*), LaForge (*66*) separated the 2-isomer by fractionation of the picrates. He obtained the 4-isomer by oxidation of the benzylpyridines to benzoylpyridines, fractionation of the picrates, and reduction of the ketones. Crook (*90*), following the work of von Braun and Pinkernelle (*86*), separated the isomers by fractional distillation. He further improved the synthesis by running the reaction in pyridine hydrochloride and adding the catalyst to the mixture before formation of the quaternary salt, obtaining a 75% yield of a mixture of 2- and 4-benzylpyridines, 90% of which was separated into the two isomers by fractionation.

The preparation of a mixture of 2- and 4-benzylpyridines on a plant scale has been described (*91*).

3-Benzylpyridine is not obtained by this method. It has been prepared by La Forge by the reduction of α-phenyl-3-pyridinemethanol (*66*).

d. Catalytic Alkylation

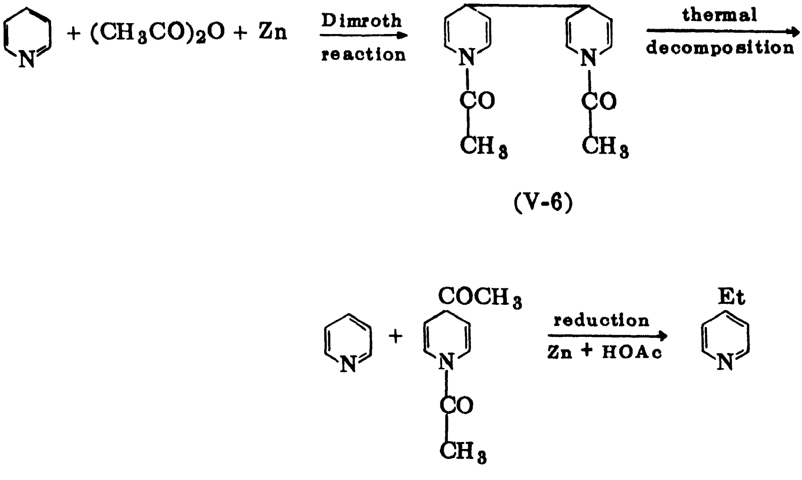
The need for large amounts of 3-picoline led Cullinane *et al.* (*92*) to seek a catalytic method for its preparation from pyridine. The vapor phase reaction of methanol with pyridine was tried over alumina and aluminum silicate catalysts at 300–500° C. The higher temperature ranges were better. At best, about 60% of the pyridine was recovered unchanged and the yield of 3-picoline was low, about 8%. Furthermore, nearly equal amounts of 2-picoline, 4-picoline, 2,6-lutidine, and other lutidines were formed. Hexamethylbenzene was also obtained.

The reaction of acids and their lead salts with pyridine at 80–120° in the presence of a catalyst which possesses an active hydrogen, for example, methanol, has yielded alkylpyridines (*93*). Acetic acid and lead acetate gave a mixture of 2- and 4-picolines, 2,4-lutidine, and 2,4,6-collidine. Propionic acid and lead propionate gave 2-ethylpyridine. Alkylpyridines (for example, 4-picoline) can be further alkylated by this method. Yields were not given for the reactions.

e. Wibaut-Arens Alkylation

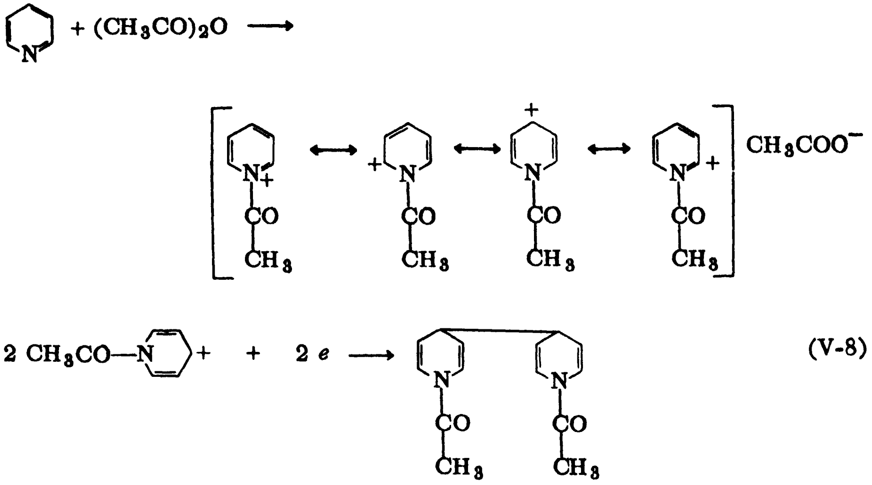
4-Alkylpyridines can be synthesized directly from pyridine by the Wibaut-Arens alkylation. The synthesis, first described by Dohrn and Horsters (*94*) and more fully investigated by Wibaut and Arens (*95,96*) and Emmert and Wolpert (*97*), involves the reaction of pyridine with an acid anhydride (Dimroth reaction) followed by a rearrangement to a 1,4-diacyl-1,4-dihydropyridine and reduction of this compound to a 4-alkylpyridine. The steps are outlined (V-5) for the formation of 4-ethylpyridine.

Compound V-7, its partially reduced derivative, 1-acetyl-4-ethyl-1,4-dihydropyridine, and 2,3-bis(4-pyridyl)butane have all been isolated from the reaction mixture (*95*). The mechanism of the dissociation of V-6 has been investigated by Frank *et al.* (*98*).



(V-5)

A possible mechanism (V-8) for this reaction has been postulated by Mosher (*99*). This mechanism does not explain the sole formation of the 4-substituted compound, but rather would indicate the formation of both 2- and 4-isomers.



(V-8)

The steps in the preparation of 4-ethylpyridine have been combined, without isolation of the intermediates, to give a suitable laboratory preparation in about 40% yield based upon the initial amount of pyridine (*95,100*). It should be noted that half the pyridine is regenerated (V-5), so the yield is 80% of that theoretically obtainable.

The commercial need for 4-ethylpyridine has led to a modification of this procedure. Iron replaces the costlier zinc as a reducing agent without any change in yield (*101*). In addition a continuous process has been developed whereby the recovered pyridine is recycled into the reaction mixture. In this manner yields of up to 71% of the theoretical have been obtained (*102*).

The reaction can be applied to higher homologs of acetic anhydride: 4-propyl-, 4-butyl-, 4-*i*-butyl-, 4-*i*-amyl-, and 4-octylpyridines have been obtained (*96,101*). The yields fall off sharply with the higher homologs, dropping to 7% of theory for the octyl derivative (*96*).

A similar reaction has been used to prepare ethyl isonicotinate from pyridine and ethyl chloroformate (*103*).

2-Alkyl and other 2-substituted pyridines do not lend themselves to this reaction. Solomon (*89*) found that the reaction fails with propionic anhydride and 2-picoline, ethyl picolinate, picolinamide, picolinonitrile, 2-aminopyridine, 2-stilbazole, and 2-chloropyridine. It also fails, contrary to Dohrn and Horsters (*94*), with acetic anhydride and 2-picoline; however, Wibaut and van der Vennen (*104*) obtained a very small yield of 4-ethyl-2-picoline but concluded that the method was not suitable for its preparation. 5-Ethyl-2-picoline gave a very low yield of 4,5-diethyl-2-picoline (*105*).

3-Picoline was successfully alkylated by Wibaut and Vromen (*106*), giving 4-ethyl-, 4-propyl-, and 4-butyl-3-picolines in yields lower than for the corresponding pyridine derivatives.

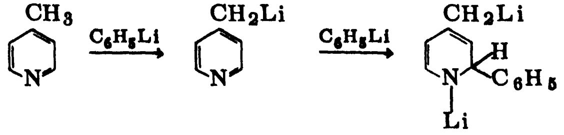
f. Alkylations Involving Organometallic Derivatives

Organometallic compounds find wide use in the preparation of alkylpyridines.

Picolines are readily metallated laterally: the products react with alkyl halides to split out metal halide and form alkylpyridines.

2-Picoline reacts with phenyllithium to yield 2-picolyllithium (*107,108*); this reacts with benzyl chloride to give 2-phenethylpyridine (*107*). Substituents on the pyridine ring such as 5-methoxyl or 5-nitro do not interfere with the alkylation of 2-picolyllithium (*109*). Long chain halides have been used without difficulty, although in the alkylation of 2-picolyllithium with 11-ethoxyundecyl bromide some 1,12-bis(2-pyridyl)dodecane was formed (*110*). 2-Phenylalkylpyridines have been prepared from 2-picolyllithium and phenylalkyl bromides (*553*). A series of 2,2′-polymethylenebipyridines was obtained from 2-picolyllithium and polymethylene dibromides. 4-Picolyllithium does not react as smoothly in this reaction (*111*). A 3-benzyloxymethyl-2-picolyllithium compound has been reported to split out the elements of lithium benzyloxide with resultant polymerization (*112*).

When the same reaction was first applied to 4-picoline, the desired 4-substituted pyridines were not obtained. This was probably due to the competing reaction (V-9); the difficulty has been resolved



(V-9)

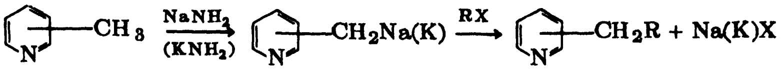
by Wibaut and Hey (*113*) who found that since the first step, the formation of the picolyllithium, is more rapid than the second, the addition of the phenyllithium to the >C=N— bond, the very slow addition of phenyllithium to 4-picoline will give 4-picolyllithium without the secondary addition. Following this procedure they were able to prepare 4-alkylpyridines containing 3–10 carbon atoms. This procedure gives yields of 60% for the higher homologs as well as the lower, making it a better method than the Wibaut-Arens alkylation for the preparation of higher 4-alkylpyridines. The use of lithium diethylamide instead of phenyllithium did not improve the yields (*113*).

The reaction has been studied in detail by Osuch and Levine (*147*) who found that a 2:2:1 ratio of 2-picoline, phenyllithium, and alkyl halide gives the best yields, in some cases over 90% of theory being obtained. In the case of 4-picoline the yields were not good with phenyllithium but improved when methyllithium was used instead. Again the best results were obtained when a 2:2:1 ratio of 4-picoline, methyllithium, and alkyl halide was used. They also obtained 2,2′-dipyridylmethane and 2,2′,2″-tripyridylmethane from 2-picolyllithium and 2-bromopyridine. 2,2′-Dipyridylmethane was also obtained from 2-picolyllithium and pyridine (*147,148*).

2-Picolyllithium has been treated with bromine at –40°C. to yield 1,2-bis(2-pyridyl)ethane in about 30% yield (*114*). The same product was probably obtained by the action of oxygen on 2-picolyllithium (*115*).

The application of the Ziegler reaction to 2,6-lutidine has led to conflicting results. The preparation of 2,6-bis(phenethyl)pyridine from 2,6-lutidine, phenyllithium, and benzyl chloride by Bergmann and Rosenthal (*116*) has been questioned by DeJong and Wibaut (*117*) who showed that the product is actually 6-(dibenzylmethyl)-2-picoline. In other reactions the latter authors found that one of the methyl groups does not participate. De Jong and Wibaut (*117*) also question the 2,6-dipropylpyridine structure assigned by Bergmann and Pinchas (*118*) to the product obtained from 2,6-lutidine by the same reaction, although no contrary evidence is offered. 2,4-Lutidine is preferentially metallated on the 2-methyl group with phenyllithium (*119*).

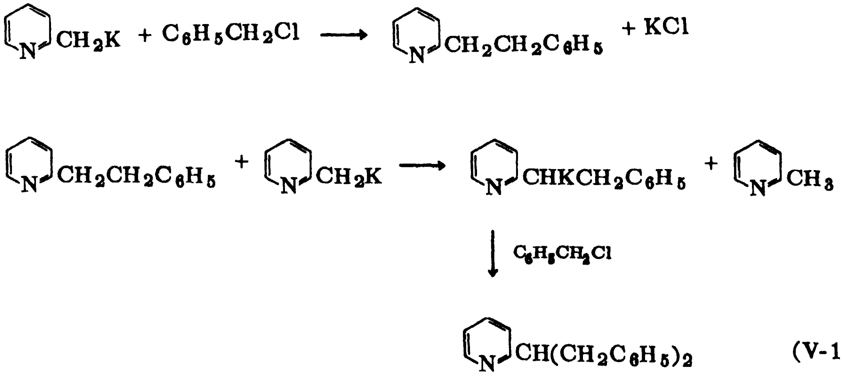
Sodium and potassium amide also metallate picolines. This reaction was first applied by Chichibabin (*120,121*). Earlier attempts had been unsuccessful (*122,123*). The metal derivative reacts with an alkyl halide to give an alkylpyridine (V-10). The reaction has



(V-10)

been carried out with aralkyl, aryl, and hetero halides and generally gives yields from 40 to 60% (*120*). Ferric nitrate has been added to the reaction mixture without apparent benefit (*37*). The reaction and its applications have been reviewed (*124–126*).

Side reactions are quaternization, elimination of hydrogen halide, and disubstitution (*120*). The disubstitution has been reduced by rapid addition of the alkylating agent to the potassium compound in liquid ammonia (*127*). This rapid addition favors the first reaction over the side reactions (V-11) (*126*). This mechanism prob-



(V-11)

ably explains disubstitution in the reactions of picolyllithium. Yields ran from 56 to 99% for the picolines, lepidine, and quinaldine, being higher for the 4-picoline than for the 2-isomer (*127*). The 4-methyl group shows the greater reactivity when the reaction is applied to 2,4-lutidine (*785*).

These higher yields with the 4-substituted pyridines when the reaction is run in liquid ammonia have been confirmed by Brown and Murphey (128). 2-Substituted pyridines gave approximately the same yields when the reaction was run at 15–20°C. as in liquid ammonia. Higher temperatures reduced the yield.

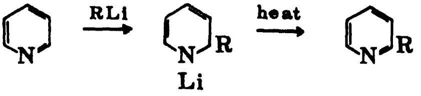
Alkyl chlorides gave better yields in this reaction than the bromides or iodides (*120*), although Brown and Murphey (*128*) obtained better yields with methyl iodide and bromide than with the chloride. Long chain halides gave low yields at room temperature, but at 100°C. 47–70% yields were obtained (*129*).

The reaction can also be applied to 2- and 4-alkylpyridines having an alpha hydrogen. In this manner branched chains were obtained. The application of the lithium method to 4-ethylpyridine and butyl bromide gave 4-(1-methylpentyl)pyridine (*113*), and 3,5-diethyl-2-propylpyridine and benzyl chloride gave 3,5-diethyl-2-(α-ethylphenethyl)pyridine (*130*). The formation of disubstituted and in some cases trisubstituted products in the Chichibabin method (*120,131*) is also due to the presence of alpha hydrogens. Use of this was also made in the preparation of 2-(1-methylcyclopentyl)-pyridine from 2-cyclopentylpyridine, sodamide, and methyl iodide (*42*). It is interesting to note that by the use of 400% excesses of sodamide and methyl iodide, isolation difficulties were avoided and a nearly quantitative yield was obtained.

4-Picolylpotassium will react with polymethylene bromides to yield 4,4′-polymethylenebipyridines. It also reacts with 4-vinylpyridine to form 4,4′-trimethylenebipyridine (*111*).

The early literature indicated that only the 2- and 4-picolines contained hydrogen sufficiently active to be replaced. The report of Brown and Murphey (*128*) that 3-picoline could also be alkylated in this manner was an extremely important contribution. It is the first example of a prototropic reaction of 3-picoline. This leads to a new method for the preparation of 3-alkylpyridines from 3-picoline (or other convenient 3-alkylpyridines). 3-Ethyl, 3-*i*-propyl, and 3-*t*-butylpyridine have been obtained by this method, the yields being lower than those for the corresponding 2- and 4-isomers. Other 3-alkylpyridines have been prepared by this method (*783–785*). The isomers gave different amounts of disubstituted products. This could probably be explained by the different degrees of stability of the reactants and products, as shown, for example, in the exchange reaction in equation V-11.

The substitution of pyridine by organolithium compounds was first reported by Ziegler and Zeiser (*132*), who prepared 2-butylpyridine and 2-phenylpyridine from butyllithium or phenyllithium and pyridine. The reaction (V-12) involves the addition of the alkyllithium to yield V-13, which on heating at 90–100°C., decomposes to give the 2-alkylpyridine. Treatment of V-13 with water gives a dihydro derivative. Only the 2-isomer was formed; none of the 4-isomer was isolated.



(V-12)

(V-13)

The reaction has also been applied to other compounds containing the >C=N— grouping, *e.g.*, quinoline, isoquinoline, and acridine (*107*). The latter adds the alkyl on the 9-carbon atom. The thermal decomposition of these other lithium derivatives is not as clean as that of the pyridine compound.

The reaction can also be applied to other alkylpyridines. 2,6-Dibutylpyridine was obtained in 67% yield from 2-butylpyridine (*107*), and 2,6-di-*t*-butylpyridine from 2-*t*-butylpyridine and 2-*t*-butyllithium (*146*). In studying the reaction of butyllithium and 4-picoline, Gilman and Broadbent (*133*) found that the alkyllithium adds at −10°C. but not at −80°C. They decomposed their addition product with carbon dioxide and then aerated the dihydro derivative to obtain 2-butyl-4-picoline. 2,3,5-Collidine was prepared in 67% yield from 3,5-lutidine and methyllithium (*112*). 3-Picoline and butyllithium gave what was apparently a mixture of 2-butyl- and 6-butyl-3-picolines (*32*).

The reaction of a Grignard reagent with an alkyl halide to produce an alkane is well known. The preparation of pyridylmagnesium bromide by Wibaut and co-workers (*134,135*) should prove useful in the synthesis of alkylpyridines; it has already been applied to the synthesis of alkenylpyridines (*136*).

The formation of 2-ethylpyridine by the reaction of ethylmagnesium bromide with pyridine as reported by Bergstrom and McAllister (*200*) could not be repeated by Goetz-Luthy (*326*). Most likely bipyridines were obtained in this reaction. Dibenzylmagnesium and benzylmagnesium chloride have been reported to react with pyridine to yield 2-benzylpyridine (*116*). This was later questioned by Veer and Goldschmidt (*137*) who reported that only 4-benzylpyridine was formed. These controversial results were resolved by Benkeser and Holton (*138*), who showed that a 1:4 ratio of the 2- to the 4-isomer is formed in the reaction of both dibenzylmagnesium and benzylmagnesium chloride with pyridine. The total yields for both methods are 32 and 8%, respectively; the higher yield may, however, be due to the use of dioxane as solvent.

2-Butyl-3-picoline has been obtained from butylmagnesium bromide and 2-bromo-3-picoline but in very low yield (*32,40*). No reaction occurred between 2-bromopyridine and *i*-butylmagnesium bromide (*40*).

An anomalous alkylation by a Grignard reagent was observed by Frank and Weatherbee; 3-acetyl-4-propylpyridine was formed from propylmagnesium bromide and nicotinonitrile (*57*).

The text and tables of Chapter VII may be consulted for further particulars on organometallic compounds of pyridine.

g. Decarboxylation Reactions

The decarboxylation of pyridinecarboxylic acids as a step in the synthesis of alkylpyridines has already been mentioned (p. 157). The removal of the carboxyl group on the side chain can also yield alkylpyridines.

Halopyridines undergo the usual reactions of halides, such as the malonic ester synthesis. These reactions frequently yield useful derivatives which may be converted to alkylpyridines by further reactions. For example, Koenigs and Jaeschke (*139*) prepared 4-propylpyridine by a malonic ester reaction with ethyl 4-chloro-2,6-pyridinedicarboxylate and subsequent hydrolysis and decarboxylation. The malonic ester reaction has also been used to increase the length of an alkyl chain by the reaction of ω-(bromoalkyl)pyridines with malonic ester (*110,276*).

2- and 4-Benzylpyridines have been obtained by the action of 2- and 4-chloropyridine on the sodium derivative of phenylacetonitrile and subsequent hydrolysis and decarboxylation. 1-Naphthaleneacetonitrile gives a similar reaction to yield 2- and 4-(1-napthylmethyl)pyridines (*140*). A similar reaction was used to prepare phenylbis(2-pyridyl)methane from 2-bromopyridine and α-phenyl-2-pyridineacetonitrile (*47*). 2-Diarylmethylpyridines have been obtained by the reaction between 2-bromopyridine and the sodium derivative of diarylacetonitriles (*334*).

Two German patents have been granted which cover the preparation of 4-alkylpyridines by the hydrolysis of 5-alkyl-5-(4-pyridyl)-barbituric acid (*141,142*). A 96% yield of 4-propylpyridine was obtained by the hydrolysis of 5-ethyl-5-(4-pyridyl)barbituric acid. Other alkyl derivatives reported were the 4-ethyl, 4-amyl, and 4-*i*-amyl. The yields were lower.

The preparation of the intermediates was not given but was probably from 4-chloropyridine and the 5-sodio derivative of the 5-alkylbarbituric acid. Probably the 4-pyridyl derivative was tried since at the time no useful method for the preparation of 4-alkylpyridines existed. 2-Alkylpyridines could probably also be prepared in this way.

h. Free Radical Reactions

Arylazotriphenylmethanes decompose on heating to yield aryltriphenylmethanes. When this reaction is run in pyridine, triphenylmethylpyridine is obtained (*143*). The exact isomer was not given and the yields were about 10%.

Triarylchloromethanes and triarylcarbinols react with 2-pyridinol to yield the 5-triarylmethyl-2-pyridinols, which may be converted to 3-triarylmethylpyridines (*144*). The reaction occurs upon heating, but the carbinol requires a trace of sulfuric acid. The yields obtained from 2-pyridinol and 3-methyl-2-pyridinol with triphenylchloromethane and diphenylxenylchloromethane were 45–60%. 6-Methyl-2-pyridinol gave a yield of only 9% when condensed with triphenylchloromethane. The authors assume that 3-substitution occurred. By usual reactions the hydroxyl group may be converted to a chloro and then to a hydrogen to give aralkylpyridines. The 3-triphenylmethylpyridine has an infrared absorption spectrum similar to tetraphenylmethane.

When diacyl peroxides are heated with pyridine and the corresponding aliphatic acids, a mixture of 2- and 4-alkylpyridines is produced (*145*). The yields are good for the lower homologs (ca. 85%) but drop to 38% with dilauroyl peroxide. The ratio of 2- to 4-isomer is about 7.6:1 for the picolines, falling to between 2:1 and 3:1 for the ethyl-, propyl-, and undecylpyridines.

Additional applications of free radical reactions are given in the section on the preparation of arylpyridines (p. 216).

i. Electrolytic Reactions

Electrolysis of aliphatic acids in pyridine forms 2- and 4-alkylpyridines with the elimination of carbon dioxide (*145*). Traces of the dialkylpyridine are sometimes obtained. The reaction is run with dry pyridine and dry acid, the water content being less than 0.5%. 2-Picoline also reacts, giving 4- and 6-alkyl-2-picolines. The yields are low and the method is not useful for preparative purposes.

The lower yields obtained by electrolysis indicate a mechanism different from the peroxide reaction previously discussed.

2. Properties and Separation of Isomers

The alkylpyridines are liquids which show the usual gradation in physical properties. The higher homologs are solids at room temperature. The 2-isomer is lower boiling than the 3- and the 4-, whose boiling points lie close together. The 4-isomer apparently has the lowest melting point, and the 2- the highest (*128*). Like pyridine, the alkylpyridines are less dense than water, the 2-alkylpyridine being less dense than the 4-isomer (*356*).

Physical properties of the alkylpyridines are summarized in Table V-4, cycloalkylpyridines in Table V-5, cycloalkenopyridines in Table V-6, and aralkylpyridines in Table V-7 (pp. 232 ff.).

The three picolines are completely miscible with water at all temperatures (*149*), contrary to earlier reports that 3-picoline was only partially miscible (*150*). In deuterium oxide only 4-picoline is completely miscible (*151*). The lutidines (*149*) and the ethylpyridines (*152*) are partially miscible. The phase relationships of these homologs with water have been correlated with their structures (*152*). The thermodynamic properties of dilute solutions of alkylpyridines in water have been discussed by Andon, Cox, and Herington (*153,154*). Data on constant boiling mixtures and densities have also been reported (*155*).

Like pyridine, the alkylpyridines form stable salts with both organic and inorganic acids. Weaker acids, for example, sodium acid succinate and sodium bisulfite, do not form stable salts with the picolines, lutidines, or collidines, but do form a salt with a stronger base such as 2,3,5,6-tetramethylpyridine (*156*). Quaternary compounds are formed with alkyl halides, and complexes with urea (*157*), tetraiodophenolphthalein (*343*), and inorganic salts such as mercuric nitrate (*327*), mercuric chloride, zinc chloride, and gold chloride. The salts and complexes are usually easily prepared and purified, and are very useful for separation and indentification. X-ray diffraction powder patterns have been used in the identification of the picrates of alkylpyridines (*158*). The heats of formation of cobalt(II) and nickel(II) oxalates and phthalates with 3- and 4-picolines have been reported (*328*). Pyridine and 3- and 4-picolines give silver(I) complexes of equal stability (*329*).

Chromium(VI) oxide forms stable 1:2 addition products with pyridine, 3-picoline, 4-picoline, quinoline, 3,5-lutidine, and 3-ethyl-4-picoline. 2-Picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine, and isoquinoline may react but oxidize on standing. 2,6-Lutidine and 2,4,6-collidine do not react (*159,160*).

Sulfur dioxide forms 1:1 addition compounds with pyridine, the picolines, and 2,3-, 2,4-, and 2,6-lutidines. 3:2 Addition compounds are also formed with 2-picoline and 2,4-lutidine, and 2:1 compounds with 4-picoline and 2,4-lutidine (*330,331*). Selenium dioxide forms compounds in a 2:1 ratio with pyridine and 3-picoline and in a 1:1 ratio with quinoline and isoquinoline (*210*). 3- and 4-Picolines may form compounds, but none could be isolated.

Dinitrogen tetroxide forms addition compounds with pyridine, quinoline, isoquinoline, acridine, 2-picoline, 3-picoline, and triethylamine in a 1:2 ratio. If the ratio of the dinitrogen tetroxide increases, the compounds become unstable. 2,6-Lutidine and quinaldine failed to give a compound under similar conditions (*336*).

The alkylpyridines are stronger bases than pyridine. This may be attributed to hyperconjugative and inductive effects. Among monosubstituted pyridines, the 2- and 4-alkylpyridines are stronger bases than the 3-substituted (*167*). The data in Table V-2 indicate that increasing numbers of alkyl groups increase the basicity; however, the effect is not additive when both alpha positions are occu-

TABLE V-2. pK_a of Alkylpyridines

Base	pK_a	Ref.
Pyridine	5.23	163
	5.17	164
	4.38[a]	146
	5.5	166
	5.30	337
2-Picoline	5.96	163
	5.97	164
	5.05[a]	146
	6.1	166
	5.95	337
2-Ethylpyridine	5.97	164
2-*n*-Propylpyridine	5.97	164
2-*i*-Propylpyridine	5.83	164
	4.82[a]	146
2-*t*-Butylpyridine	5.76	164
	4.68[a]	146
3-Picoline	5.68	164
	5.8	166
	5.85	337
	5.82	338
3-Ethylpyridine	5.70	164
3-*i*-Propylpyridine	5.72	164
3-*t*-Butylpyridine	5.82	164
4-Picoline	6.05	163
	6.02	164
	6.1	166
	6.10	337
	6.11	338
4-Ethylpyridine	6.02	164

pied, since steric factors tend to annul the inductive effects. This is indicated more pointedly in the decreasing basicity with increasing branching of the 2-alkylpyridines, the lower basicity of a 2- as compared to a 4-alkylpyridine, and the weak basicity of 2,6-di-*t*-butylpyridine. The basicities of the entire series of mono-, di-, tri-, tetra-, and pentamethylpyridines have been determined (*337*). 2,4- Dinitrobromobenzene and 2,4-dinitrochlorobenzene quaternize with alkylpyridines when the alkyl groups are in the 3 position or contain no active hydrogens when in the 2 or 4 position (*438*). 4-Picoline, 3-picoline, and pyridine react with decreasing rate with nitrochloropyridines (*439*).

TABLE V-2. (*Continued*)

Base	pK_a	Ref.
4-*t*-Butylpyridine	5.99	164
2,3-Lutidine	6.56	337
2,4-Lutidine	6.79	163
	6.80	337
2,5-Lutidine	6.55	337
2,6-Lutidine	6.62	163
	6.75	164
	6.74	165
	5.77[a]	146
	6.9	166
	6.72	337
3,4-Lutidine	6.61	337
3,5-Lutidine	6.34	337
2,6-Di-*i*-propylpyridine	5.34[a]	146
2,6-Di-*t*-butylpyridine	3.58[a]	146
2,3,4-Collidine	7.38	337
2,3,5-Collidine	7.15	337
2,3,6-Collidine	7.40	337
2,4,5-Collidine	7.28	337
2,4,6-Collidine	7.45	163
	7.59	165
	7.63	337
2,3,4,5-Tetramethylpyridine	7.78	337
2,3,4,6-Tetramethylpyridine	8.10	337
2,3,5,6-Tetramethylpyridine	7.91	337
2,3,4,5,6-Pentamethylpyridine	8.92	43
	8.75	337

[a] In 50% water-ethanol.

These steric effects also enter into the quaternization reactions. In a study of the reactions of alkyl halides with alkypyridines, Brown and Cahn (*168*) found that increasing steric requirements tend to lower the stability of the complex. Similar results are obtained with trimethylboron and pyridine, 2-picoline, and 4-picoline (*167*). The literature has been reviewed by Brown (*427*).

The basicities of the alkylpyridines do not show a linear relationship with the rates or activation energies of their reactions with methyl iodide (*164*). A linear relationship is obtained between the pK_a of these bases and ΔH for the reaction with methanesulfonic acid (*169*) and boron trifluoride (*170*). The ability to form hydrogen bonds is also linearly related to the pK_a (*171*). The pK_a of alkylpyridines has been used to calculate the partition coefficients (*166*).

The dipole moments have been determined for a number of pyridine derivatives but little data exist for the alkylpyridines. The available data are given in Table V-3. The discrepancies are probably due to both differences in methods and purity of the materials.

TABLE V-3. Dipole Moments of Alkylpyridines

Base	Moment	Ref.
2-Picoline	1.96	172
	1.92	173
	1.72	340
	1.97	550
3-Picoline	2.30	340
	2.40	550
4-Picoline	2.57	339
	2.60	550
4-Ethylpyridine	2.65	550
2,3-Lutidine	2.05	241
	2.20	550
2,4-Lutidine	2.30	550
2,5-Lutidine	2.14	241
	2.15	550
2,6-Lutidine	1.65	174
	1.87	172
	1.66	550
3,4-Lutidine	1.85	341
3,5-Lutidine	2.58	550
2-Propylpyridine	1.91	550
3-Propylpyridine	2.45	550
4-Propylpyridine	2.70	550
4-*i*-Propylpyridine	2.70	550
2,3,4-Collidine	2.11	341
2,3,6-Collidine	2.09	341
2,4,6-Collidine	2.05	174
	1.93	340
2-Butylpyridine	1.90	550
3-Butylpyridine	2.47	550
4-Butylpyridine	2.72	550
4-*s*-Butylpyridine	2.72	550
4-*t*-Butylpyridine	2.73	550
2-Pentylpyridine	1.90	550
4-Pentylpyridine	2.72	550
4-(1-Ethylpropyl)pyridine	2.74	550

Infrared spectral data have been recorded for the complete series of mono-, di-, tri-, and tetramethylpyridines except 3,4,5-collidine (*428*). Spectral data have been obtained for 2-picoline (*173,256,344–346*), 3-picoline (*256,344–346,399*), 4-picoline (*346,399*), 2,3-lutidine (*399*), 2,4-lutidine (*399*), 2,5-lutidine (*399*), 2,6-lutidine (*345,346, 399*), 2-ethylpyridine (*346*), 3-ethylpyridine (*399*), 4-ethylpyridine (*399*), 2,3,6-collidine (*399*), 2,4,6-collidine (*345,399*), 6-ethyl-2-picoline (*399*), 3-butylpyridine (*20*), 3,5-diethylpyridine (*22*), 3-ethyl-2,4-lutidine (*22*), 2-butyl-3-picoline (*32*), 6-butyl-3-picoline (*32*), and 3-triphenylmethylpyridine (*144*).

Raman spectra have been determined for 2-picoline (*347,348*), 3-picoline (*347,348*), 2,4-lutidine (*348*), 2,6-lutidine (*348*), and 2,4,6-collidine (*348*). The spectra of the hydrochlorides of these bases show differences from the spectra of the free bases (*349*).

The ultraviolet spectra of the complete series of mono-, di-, tri-, tetra-, and pentamethylpyridines have been determined (*350*). Spectral data have been obtained for 2-picoline (*173,351*), 3-picoline (*352*), 4-picoline (*75,353*), 3-ethylpyridine (*399*), 4-ethylpyridine (*353*), 2-propylpyridine (*37*), 2-cyclopropylpyridine (*37*), 3-butylpyridine (*20*), 3,5-diethylpyridine (*22*), 3-ethyl-2,4-lutidine (*22*), pentamethylpyridine (*43*), 2,4-dimethyl-6-(2,6-dimethylheptyl)pyridine (*358*), 2,4-dimethyl-6-(2,6,6-trimethylcyclohexenyl)pyridine (*358*), 2,4-dimethyl-6-[3-(2,4,4-trimethylcyclohexenyl)]pyridine (*358*), *cis-* and *trans*-2,4-dimethyl-6-(2,2,6-trimethylcyclohexyl)pyridine (*358*), and 2- and 4-benzylpyridines (*433*).

Data for the heats of fusion and vaporization have been obtained for the three picolines and 2,6-lutidine (*354*).

The biological properties of the alkylpyridines have been summarized (*355*). The industrial and biological properties of the higher alkylpyridines have been reviewed (*356*). Alkylpyridines have been tested as fumigants. The 4-alkylpyridines were more active than the 2-isomers, the propyl and butyl derivatives being most active (*175*).

The procedures employed in the separation and purification of the individual alkylpyridines may be based on (1) differences in physical properties of the free bases and their derivatives or (2) differences in chemical reactivity.

From coal tar fractions which boil below 230°C. the bases are extracted with dilute sulfuric acid and then recovered by alkalization. Before separation the bases may be further purified by refluxing with dilute alkali (*360*), or better by addition of a small amount of permaganate (*359*). This serves to remove pyrrole and its derivatives, hydrocyanic acid, and sulfur compounds, and gives color-stable bases.

From the lower boiling fractions pyridine and 2-picoline can be separated by careful fractionation. 2-Picoline has been obtained in 99.76% purity by fractionation (*173*). Before the development of efficient fractionating columns, salts were used to separate the two bases. For example, the perchlorate of pyridine is insoluble (*361*) and may be used in the determination of pyridine in mixtures of bases (*362,363*). Polyhalophenols have also been used in the separation (*382*).

The fraction of b.p. 140–145°C. contains 3-picoline, 4-picoline, and 2,6-lutidine and has been extensively studied as a commercial source of 3-picoline for the manufacture of niacinamide.

Salts and addition compounds have been used frequently in the separation of the components of the "beta-picoline" fraction. 2,6-Lutidine forms an insoluble urea complex and can thus be separated from the picolines (*377,378*). 2,6-Lutidine and sulfurous acid give a nonvolatile salt from which the picolines can be distilled (*418*). Dinitrochlorobenzene gives complexes with 3-substituted pyridines but not with the 2- and 4-isomers. 3-Picoline can thus be separated (*424*). 4-Picoline forms a calcium chloride adduct of low volatility, which can be separated by dry distillation from 3-picoline, 2,6-lutidine, and pyrrole (*379*); or the 2,6-lutidine can first be removed and then use made of calcium chloride (*236,380*). In a similar manner zinc chloride (*380,381*) forms complexes with the picolines, and cupric sulfate with 3-picoline (*383*). Zinc chloride has been used to separate pyridine bases from pyrrole (*357*). The oxalates (*384*), phosphates (*385*), and ethyl-*p*-toluenesulfonates (*386*) show differences in solubilities. Improvements in the use of oxalates have resulted in a good separation of 4-picoline (*410*). The hydrochlorides of 3- and 4-picolines and 2,6-lutidine prove useful in separating the bases. 2,6-Lutidine hydrochloride is less soluble than the others in

2-propanol (*387*). A separation in two stages yielding 2,6-lutidine hydrochloride and then 4-picoline hydrochloride may be effected in hydrocarbon solvents (*388*).

Separation has been made by fractional crystallization of the molten hydrochlorides (*390*). The fractional distillation of the hydrochlorides is a convenient way of separating these bases but is not commercially feasible because of corrosion problems (*389,391*). The fractionation of benzoates (*393*), substituted benzoates (*394*), and phenolates (*395*) has also been used.

The use of azeotropes has proved convenient in separating the bases in the "beta-picoline" fraction. Lower fatty acids (*400–402*), phenol (*403*), *o*-chlorophenol (*404*), and water (*405*) have been used. The requirements for entrainers used in azeotropic dehydration of pyridine bases have been discussed (*406*). Pyrrole has been removed from the pyridine bases as a water azeotrope (*409*).

The 3- and 4-picolines and 2,6-lutidine have also been separated by fractional crystallization of the bases (*407,408*).

Various combinations of the above methods have been used to achieve separations (*411*).

Based on specific gravity and cloud point, a method has been developed for the analyses of the components of the "beta-picoline" fraction (*364*).

The "lutidine" fraction from coal tar bases has a boiling point range of 155–161°C. By using methods similar to those outlined for the "beta-picoline" fraction it has been possible to separate the "lutidine" fraction into the following components: 2,3-lutidine, 2,4-lutidine, 2,6-lutidine, and 6-ethyl-2-picoline (*399,412,413,415*). The components have also been separated by way of their 1-oxides (*365*).

The "collidine" fraction boiling at 170–173°C has been separated into 3-ethylpyridine, 2,3,6-collidine, and 2,4,6-collidine (*399, 414*).

Infrared absorption spectroscopy provides convenient methods for the analysis of the picoline, lutidine, and collidine fractions (*399*).

Paper chromatography (*419–421*), gas-liquid partition chromatography (*422*), and ion-exchange resins (*423*) have been used. Although paper chromatography gives a separation, it is not commercially feasible. The other two methods did not give good separations.

Various methods have given 2-, 3-, and 4-picolines and 2,6-lutidine of purity greater than 99.7% (*354*), and 2,6-lutidine and 2,4,6-collidine of 99% purity (*165*).

A large number of chemical purification methods have been developed, but these are not too useful since they frequently destroy both the 4-picoline and 2,6-lutidine. They are based on the relatively greater reactivity of 2- and 4-alkylpyridines as compared with the 3-alkyl compounds. Among these methods are the Mannich reactions of 4-picoline and 2,6-lutidine (*392*) and their reactions with phthalic anhydride (*366,367,417*) (this reaction may also be used as a test for the purity of 3-picoline, which does not give the yellow pyrophthalone precipitate), with ketene (*368*), with furfuraldehyde and benzaldehyde (*369*), with sulfur (*370*), with formaldehyde (*371, 372*) and with oxides, oxyhalides, or halides of sulfur or phosphorus (*373*). 4-Picoline and 2,6-lutidine may be oxidized preferentially with selenium dioxide (*376*) or in the vapor phase using metal oxide catalysts (*374,375*). The pyrophthalone method has also been used to separate 2- and 3-picolines (*416*).

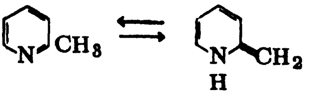
The isolation and purification of the alkylpyridines are also reviewed in Chapter II (pp. 113–124).

3. Reactions

The alpha hydrogen in 2- and 4-alkylpyridines is very reactive, giving rise to prototropic reactions. The 3-alkylpyridines are not as reactive; however, this difference, as previously shown for the reaction of the picolines with metallo compounds, is quantitative and not qualitative (*128*). 3-Picoline possesses greater prototropic activity than toluene. This has been discussed by Dewar and can be explained by an inductometric effect. The basic strengths of the picolines can also be explained by this effect (*181,182*).

The activity of the methyl hydrogens in the methyl homologs has been investigated by Ploquin using a Tschugaeff reaction with methylmagnesium iodide (*398*). The picolines and 2,4-, 2,5-, and

2,6-lutidines have no activity. 2,3-Lutidine has only 1% activity. The collidines possess higher activity, with 2,4,5-collidine having 76% at 100°C. Ploquin attributes the activity to hyperconjugation effects and not to tautomerism (V-14). Additional evidence against the existence of V-15 is available from spectral data (*256,344,351*).



(V-14)

(V-15)

a. Isomerization

The alkyl group in the 2 and 4 positions is labile relative to the 3 position. Mixtures containing the 2- and 4-picolines, 2,4- and 2,6-lutidines, and 2,4,6-collidine may be converted to 3-picoline or a lutidine containing a 3-methyl group by heating at 500°C. in either liquid or vapor phase in the presence of a catalyst such as chromium oxide. The yields are not quantitative, and separations of the products and reactants are required (*183*). The 3-picoline which is obtained is a valuable intermediate, particularly for the synthesis of niacin.

b. Dealkylation

The dealkylation reactions yield pyridine from its homologs, in most cases by hydrogenolysis Pyridine homologs can be hydrogenated at temperatures from 600 to 900°C. to yield pyridine (*184*). Higher temperatures favor ring hydrogenation. In the presence of hydrogenation catalysts, such as nickel–aluminum oxide, the temperatures can be lowered to 250–600°C (*184*). The detrimental effect of iron can be avoided by treatment of the equipment with sulfur, selenium, or their compounds (*185*). Similar reactions have been carried out with the homologs of quinoline and thiophene (*186*). 2-Picoline gives better yields than the higher homologs at 800°C. in the presence of hydrogen sulfide (*187*).

Use is made of the hydrogenolytic cleavage in the removal of pyridine bases contained in hydrocarbon oils. The higher boiling homologs, which are difficult to separate from the hydrocarbon oil, are first cleaved to the lower boiling pyridine, picolines, and lutidines by hydrogenolysis at 800–1200°F. under pressure and then easily extracted with dilute acid (*275*).

2-Picoline has been dealkylated by heating in the presence of silver acetate (*188*). Pyridine and ethylbenzene are given by a high-temperature high-pressure exchange reaction between the isomeric ethylpyridines and benzene over clay catalysts. Recycling is required since conversions are not high (*189*).

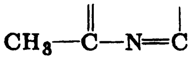
c. *Oxidation*

The alkylpyridines, like the alkylbenzenes, can be oxidized with a wide variety of oxidizing agents to give aldehydes, carboxylic acids, or in some reactions potential carboxylic acids.

The ozonolysis of pyridine and alkylpyridines results in the destruction of the ring to yield a series of aldehydes, ketones, and acids. The acids are usually obtained in the form of their amides (*190–192*). (Similar results are obtained in the benzene series except that amides are not formed.) The products correspond to both arrangements of the double bonds in the Körner-Dewar pyridine structures, analogous to the Kekulé structures for benzene.

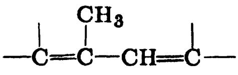
The reaction is of value in the elucidation of the structures of alkylpyridines (*190–194*). The different products may be correlated with different structural units; for example:

Acetic acid



$\mathrm{CH_3{-}\overset{\|}{C}{-}N{=}\overset{|}{C}}$

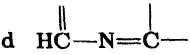
Pyruvic acid



$\mathrm{-\overset{|}{C}{=}\overset{\overset{CH_3}{|}}{C}{-}CH{=}\overset{|}{C}{-}}$

Glyoxal $\mathrm{{=}CH{-}CH{=}}$

Formic acid



$\mathrm{H\overset{\|}{C}{-}N{=}\overset{|}{C}{-}}$

The reaction has to be run at about –30 C. to avoid the formation of secondary oxidation products.

Like their benzene analogs, the alkylpyridines can be oxidized to the corresponding acids with potassium permanganate. The reaction is best run in dilute aqueous solution with gradual addition of the oxidizing agent at temperatures increasing from 70 to 90°C. (*195*). 5-Ethyl-3-picoline and 5-ethyl-2-picoline give, respectively, 5-methylnicotinic acid (*196*) and 6-methylnicotinic acid (*197*). A similar result has been observed by the author for the nitric acid oxidation of 5-ethyl-2-picoline (*198*).

Benzylpyridines have been oxidized by permanganate to benzoylpyridines (*85,199,201*). Sodium hypochlorite does not oxidize the methylene group in benzylpyridines (*201*).

Permanganate in acidic solution destroys the ring, oxidizing pyridine and its homologs to carbon dioxide and aliphatic acids (*202*). A nitro group apparently activates an alkyl group in the position para to itself. It is believed that the permanganate oxidation of 3-nitro-2,4,6-collidine gives 4,6-dimethyl-5-nitropicolinic acid (*203*). Manganese dioxide and sulfuric acid oxidize picolines to carboxylic acids (*529*). 3-Picoline is oxidized by nitric acid to nicotinic acid. Nitric acid of density 1.4 gives better yields than more concentrated acid. A mercuric nitrate catalyst was used (*204*). The nitric acid oxidation of 5-ethyl-2-picoline to 6-methylnicotinic acid has been mentioned (*198*). The same compound gave isocinchomeronic acid when the reaction was run under pressure (*205*). The oxidation of alkylpyridines with nitric acid under pressure yields nicotinic acid from 3-picoline and isonicotinic acid from 4-picoline, 4-ethylpyridine 2,4-lutidine, and 2,4,6-collidine (*396*).

Selenium dioxide, as would be expected from its oxidation of active methylene groups (*206*), readily attacks methyl groups in the 2 and 4 positions. 2-Picoline and 2,6-lutidine are oxidized to picolinic and dipicolinic acids, respectively, by refluxing with selenium dioxide. Only very small yields of aldehydes were obtained (*207*). Similar results were also obtained with quinoline homologs (*207*). The results with 2-picoline have been confirmed (*208–210*). 4-Picoline has been oxidized to isonicotinic acid (*209–211*); this reaction gives higher yields than the oxidation of 2-picoline.

The results with 3-picoline are conflicting. Henze (*207*) obtained some nicotinic acid when he refluxed the reactants in xylene; however, Cook and Yunghans could not oxidize 3-picoline in boiling diphenyl ether (*209*).

In the presence of sulfuric acid, selenium can be used in catalytic amounts, since it is re-oxidized by the sulfuric acid above 260°C. In this way many pyridine bases and quinoline have been oxidized to nicotinic acid at temperatures from 260 to over 300°C (*212–214*).

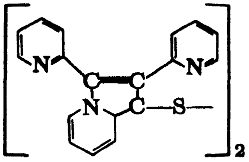
At higher temperatures decarboxylation of 2- and 4-carboxyl groups gives nicotinic acid as the major product (*214*).

The catalytic vapor-phase oxidation of alkylpyridines has been investigated rather thoroughly since it is potentially the cheapest method of oxidation (*215*). The products obtained depend upon the air to base ratio. A deficiency of air yields pyridoins (*216,217*); a larger amount produces aldehydes (*216*); and an excess gives carboxylic acids (*216*). A study of the oxidation of 2,4-lutidine and 2,4,6-collidine indicated that all possible combinations of mono- and dialdehydic derivatives were formed. The expected tricarboxaldehyde from 2,4,6-collidine was not obtained (*218*).

Vapor-phase oxidation in the presence of ammonia gives cyanopyridines (*219*). It is probable than an amide is first formed and then dehydrated to yield a nitrile. The isolation of amides has been reported (*220*).

The formation of 1,2-bis(4-pyridyl)ethane by the action of sulfur on 4-picoline has been reported (*76*). In this reaction 1,2-bis(4-pyridyl)ethylene, 1,2,3-tris(4-pyridyl)propane, 2,3,4,5-tetrakis(4-pyridyl)thiophene, and hydrogen sulfide were also formed. The yield of the thiophene is increased by the addition of alkali (*76,221*).

The reaction of 2-picoline with sulfur follows a different course, giving 1,2-bis(2-pyridyl)ethane and more complex products (*222*), one of which was shown by Emmert and Groll (*223*) to be V-16.



(V-16)

2-Picoline reacts with sulfur in the presence of aniline (Willgerodt reaction) to yield thiopicolinanilide and 2-(2-pyridyl)benzothiazole (*224,225*). 2-(2-Pyridyl)naphthothiazole was obtained when β-naphthylamine was used (*224*). 4-Picoline gave similar compounds and *N,N'*-diphenylisonicotinic acid amidine in addition (*226*). No identifiable product was obtained from 3-picoline, but 4-*n*-propylpyridine gave 2-(β-4-pyridylethyl)benzothiazole (*255*).

In the Willgerodt reaction, 4-picoline and 4-ethylpyridine gave higher yields than 2-picoline (*225*).

A low yield of picolinic acid was obtained in a photochemical oxidation of 2-picoline in sunlight (*227*). Similar low yields were obtained from the photochemical oxidation of 2-benzylpyridine to 2-benzoylpyridine (*228*).

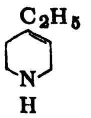
3-Picoline has been converted to nicotinic acid by electrolytic oxidation (*229*). 4-Picoline gave a low yield of isonicotinaldehyde (*397*). 2-Benzylpyridine has been oxidized in about 66% yield to 2-(α-hydroxybenzyl)pyridine by mercuric acetate (*230*).

The preparation of pyridinecarboxylic acids by side-chain oxidation is further discussed in Chapter X.

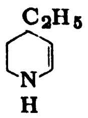
d. Nuclear Reduction

Pyridine, 2-picoline, 3-picoline, 2,6-lutidine, and 2,4,6-collidine have been catalytically reduced over platinum oxide to the corresponding piperidine derivatives (*231*). Rate studies indicate that 2-picoline, 2-ethylpyridine, and 2-propylpyridine are reduced about half as fast as pyridine. Similar results were obtained with mixtures (*232,425,426*). 2-Picoline gave 2-pipecoline in 70% yield with a palladium catalyst (*233*) and in 80% yield with a Raney nickel catalyst (*234*).

Sodium and butanol reduced 4-ethylpyridine, 4-*n*-propylpyridine, 4-*n*-butylpyridine, 4-ethyl-2-picoline, 4-ethyl-3-picoline, and 4-ethyl-2,6-lutidine to their tetrahydro derivatives (*235*). The structure of the ethyl derivative was established as 4-ethyl-1,2,5,6-tetrahydropyridine (V-17), since it formed a benzenesulfonamide stable to alkali.



(V-17)



(V-18)

The other possibility, the 1,2,3,4-tetrahydro derivative, would be unstable under these conditions because of its vinylamine structure (V-18).

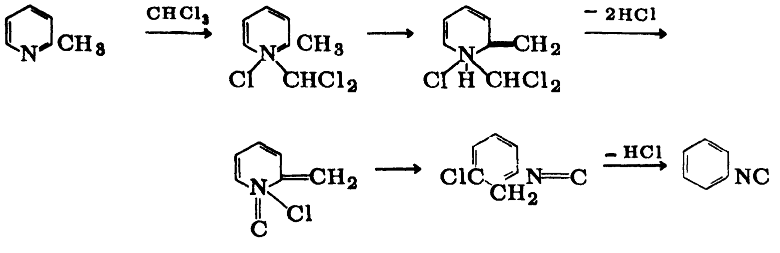
Polarographic reduction studies gave the following half-wave potentials: pyridine, 1.73; 3-picoline, 1.72; 4-picoline, 1.83; and 2,6-lutidine, 1.78 (*236*).

Lukeš and his group have reduced the 1-methylpyridinium, 1-methyl-3-picolinium, and 1-methyllutidinium formates to yield 1-methylpiperidine and 1-methyltetrahydropyridine derivatives as well as aliphatic products of ring cleavage (*237,238*).

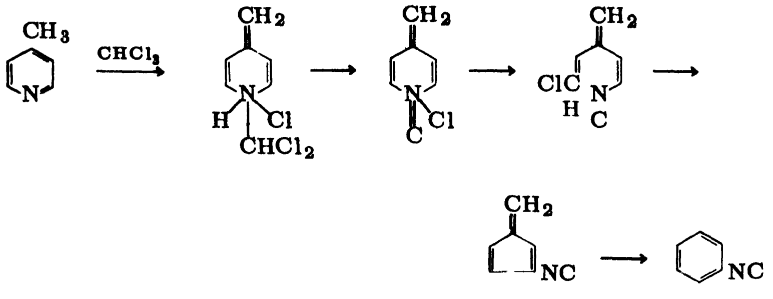
The pyridine nucleus is more readily reduced than the phenyl, as shown by the formation of aralkylpiperidines from aralkylpyridines (*231,239*) and of phenylpiperidines from phenylpyridines (*231*).

e. Ring-Opening Reactions

Homologs of pyridine and quinoline containing a methyl group in the 2 or 4 position react with chloroform or bromoform in strongly alkaline solution to give a positive carbylamine test (*240*). Compounds with methyl groups in the 3 or 5 position do not give this test. The proposed mechanism for 2-picoline is given in equation V-19. The final products are aromatic, as evidenced by hydrolysis to anilines. Both 2- and 4-picolines give the same final product. A possible mechanism for the reaction of 4-picoline is given in equation V-20 (*240*). The substituted picolines yield a



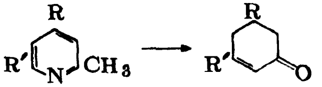
(V-19)



(V-20)

series of substituted carbylamines; for example, where RNC is the product, R is *m*-tolyl for 2,6-lutidine, *p*-tolyl for 2,5-lutidine, a mixture of *m*- and *p*-tolyl for 2,4-lutidine, *o*-tolyl for 2,3-lutidine, and a mixture of *o*- and *m*-tolyl for 3,4-lutidine. The collidines yield xylyl derivatives and quinaldine a β-naphthyl derivative.

Reduction of 2-picoline with sodium and ethanol in liquid ammonia, followed by refluxing with dilute acid, yields cyclohexenone derivatives (*241*). The dihydropyridine is first formed and then hydrolyzed and cyclized to yield the cyclohexenones in up to 30% yield (V-21).



(V-21)

The photolysis of pyridine to colored aldehydic derivatives is also shown by 2-benzylpyridine (*161,162*), the picolines, 2,4-lutidine, and 2,6-lutidine (*162*), but 2,4,6-collidine did not react like pyridine (*162*).

f. Side-Chain Halogenation and Other Substitution

The homologs of pyridine can be brominated in the side chain (*245*). 3-Picoline and 5-ethyl-2-picoline react with bromine to form 3-bromomethylpyridine and 5-(α-bromoethyl)-2-picoline, respectively (*245*). 4-Picoline has been brominated in glacial acetic acid to yield a tribromo derivative. However, it is not a simple tribromomethyl compound since it failed to hydrolyze to isonicotinic acid (*246*).

N-Bromosuccinimide in the presence of benzoyl peroxide brominated 2-picoline to a mixture of mono- and dibromo products. 4-Chloro-2-picoline gave similar results, while 4-chloro-2,6-lutidine gave a mixture of mono- and dibromo derivatives where one or both methyl groups were substituted (*247*). Investigation of a similar bromination of 2,4-lutidine, 6-amino-2,4-lutidine, and 4,6-dimethyl-2-pyridinol showed that only the last compound was attacked in the side chain, and then only in the presence of large concentrations of benzoyl peroxide (*248*).

2-Picoline has been chlorinated to 2-trichloromethylpyridine. It was not possible to control the reaction to give the monochloro or dichloro derivative (*249*). In the presence of ultraviolet light, 3-

picoline has been chlorinated to 3-trichloromethylpyridine, which is readily hydrolyzed to nicotinic acid (*250*). Under these conditions 3-ethylpyridine and 5-ethyl-2-picoline gave 3-(trichloroacetyl)pyridine and 5-(trichloroacetyl)-2-picoline, respectively (*251*). Complete chlorination of the ethyl group was followed by hydrolysis of the α-chlorine atoms.

Chlorination of 2-picoline in the light at low temperatures and then at higher temperatures gave mixtures of 2-trichloromethylpyridine and its ring-chlorinated derivatives (*252,253*). 3-Picoline and 4-picoline gave no identifiable products. 2,4-Lutidine and 2,6-lutidine were chlorinated under similar conditions to give 2,4- and 2,6-bis(trichloromethyl)pyridines as well as their monochloro ring derivatives.

Higher homologs of pyridine nitrate in the side chain (*254*). 2-*i*-Butyl-3,5-di(*i*-propyl)pyridine gave what is probably 2-*i*-butyl-3,5-di-(α-nitro-*i*-propyl)pyridine (*255*).

g. Nuclear Substitution

Although pyridine is nitrated with great difficulty and requires vapor phase treatment at high temperatures to give even low yields, alkylpyridines are more readily nitrated, especially with increasing numbers of alkyl groups. Thus 2,4,6-collidine with potassium nitrate in fuming sulfuric acid gave a yield of almost 90% of mononitro derivative (*257*). Absolute nitric acid does not give good yields (*258*). 2,6-Lutidine requires more drastic conditions to give a 66% yield of a mononitro derivative (*257*). Both pyridine and 2-picoline gave low yields (*257*). (*Cf.* pp. 470 f. and 496.)

The 2- and 4-benzylpyridines are nitrated in the benzene ring in the *p*-position. Further nitration introduces a second nitro group in the *o*-position (*259,260,429*). 2-Phenethylpyridine gives a mixture of *p*- (64% yield), *m*-, and *o*-nitrophenyl derivatives (*317*).

The 2- and 4-picolines have been sulfonated like pyridine, using a mercury catalyst and fuming sulfuric acid (*261*). A comparison of the sulfonation of pyridine and the picolines indicated lower yields for the 2-picoline (*262*) and 4-picoline (*262,263*) with very low yields for 3-picoline (*262*). Although it has been reported that 5-ethyl-2-

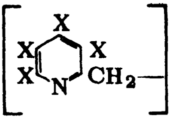
picoline can be sulfonated in this manner (*261*), the author has been unable to obtain the product. Considerable tarring occurred and a large amount of starting material was recovered (*264*). Sulfonation is further discussed in Chapter XV.

2-Picoline has been iodinated with iodine in fuming sulfuric acid to give 5-iodo-2-picoline (*265*). 4-Picoline gave 3-iodo-4-picoline (*266*) and 2,4,6-collidine gave a mixture of 3-iodo-2,4,6-collidine and what is probably 3,5-diiodo-2,4,6-collidine (*266*). Halogenation is further discussed in Chapter VI (pp. 301 ff.).

The Friedel-Crafts reaction with benzylpyridines results in the substitution of the benzene ring. 2-(*p*-Acetylbenzyl)pyridine has been obtained from 2-benzylpyridine and acetyl chloride (*430*).

The alkylpyridines upon treatment with sodium amide or sodium in liquid ammonia yield 2-amino derivatives (*267*). When both the 2 and 6 positions are occupied, for example, in 2,6-lutidine, the 4 position is substituted and 4-amino-2,6-lutidine is obtained (*268*). 3-Picoline gave a mixture of 2-amino-3-picoline and 6-amino-3-picoline (*269*), although Seide obtained only the former (*270*).

Diamination may occur at higher temperatures. Thus 2-picoline gave a mixture of 3,6-diamino-2-picoline and 4,6-diamino-2-picoline (*271*). The formation of bipyridines as by-products has been reported (*272,273*). A material analyzing for a multiple of V-22 has been isolated from the amination of alkylpyridines (*274*). The amination reaction is further discussed in Chapter IX.



X = H or methyl

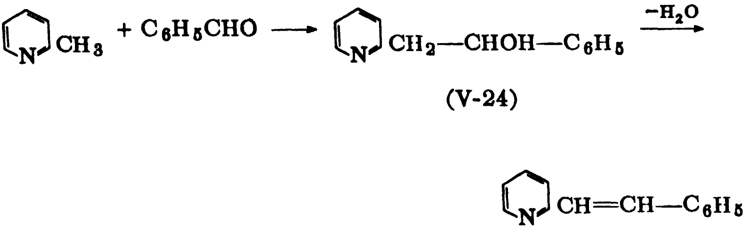
(V-22)

h. Condensation Reactions

2-Picoline, like toluene, condenses with butadiene in the presence of sodium. A mixture of 2-(3-pentenyl)pyridine and 2-[1-(2-butenyl)-3-pentenyl]pyridine was obtained. Styrene and 2-picoline gave 2-(3-phenylpropyl)pyridine (*179*). Similar condensations between 2-picoline and 2-vinylpyridine in the presence of sodium (*519*), and 4-picoline and 4-vinylpyridine in the presence of potassium (*111*), gave 2,2′-trimethylenebipyridine and 4,4′-trimethylenebipyridine, respectively.

2- or 4-Alkylpyridines containing alpha hydrogen undergo aldol condensations with carbonyl compounds to yield alcohols or unsaturated compounds, depending upon conditions. The reaction was first studied by Baurath (*277*) and since then numerous studies have been made.

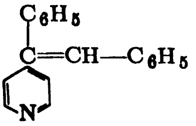
Benzaldehyde condenses with 2- or 4-picoline to yield 2- or 4-stilbazole (V-23). The intermediate alkine (V-24) may be formed by first heating in water, and is converted to the stilbazole by heating with acetic anhydride (*278,279*). The stilbazoles are formed directly when the reaction is carried out in the presence of zinc chloride (*277*) or acetic anhydride (*280*). The 2- and 4-picoline alkiodides react with the aldehydes in the absence of a catalyst (*281*). The alkine reaction is reversible and the starting materials may be obtained (*279*). (*Cf.* Chapter XIII (Table XIII-1).)



(V-24)

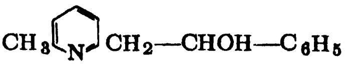
(V-23)

The reaction is applicable to higher homologs. 2,6-Lutidine and 2,4,6-collidine form 2,6-distyrylpyridine (*282*) and 2,4,6-tristyrylpyridine (*283*), respectively. 4-Benzylpyridine reacts with benzaldehyde to yield V-25 (*284*). The 3-methyl group does not react, as seen in the conversion of 2,3-lutidine to a series of 3-methyl-2-stilbazoles (*278*). Cinnamaldehyde (*285*) and isatin (*286*) also react.

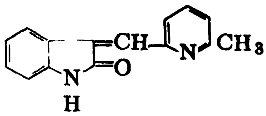


(V-25)

The methyl groups in 2,6-lutidine react stepwise. Mixtures of mono- and distyryl derivatives were obtained from 2,6-lutidine and *p*-hydroxy- and *p*-nitrobenzaldehydes (*118*). 2,6-Lutidine reacted with benzaldehyde in the presence of water under pressure to give V-26 (*287*), and with isatin to give V-27 (286).



(V-26)

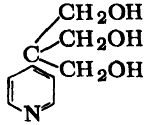


(V-27)

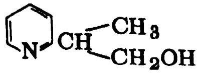
The reactivity of the methyl group toward *o*- and *m*-nitrobenzaldehydes has been compared for 4-picoline and a series of analogous compounds such as 4-methylquinoline, 4-methylbenzoquinolines, 9-methylacridines, etc. The benzoquinolines were the most active. Only 9-methylacridine was less active than 4-picoline (*288*).

The nitro group in 3-nitro-2,4,6-collidine activates the *p*-methyl group, 4,6-dimethyl-5-nitro-2-stilbazole being obtained from the reaction with benzaldehyde (*203*).

Formaldehyde reacts with 2- and 4-alkylpyridines to give 2- and 4-pyridineethanols. These can then be dehydrated to unsaturated compounds. All α-hydrogens may be replaced to give a trimethylol derivative (V-28) (*290*). 2-Ethylpyridine gives V-29 (*289*). Two



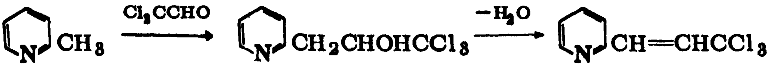
(V-28)



(V-29)

molecules of 2-picoline react with a molecule of formaldehyde to give trimethylenebipyridine (*78*). The 4-methyl group in 2-4-lutidine reacts preferentially, giving the 4-ethanol (*291*). However, the 2-methyl group reacted in 2,4,6-collidine and 5-nitro-2,4,6-collidine (*292*). Mixtures of the monomethylol and dimethylol derivatives were obtained when formalin was refluxed with 4-ethylpyridine (*293*). Paraformaldehyde has been used in place of formalin (*294*).

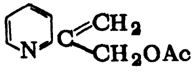
Chloral condenses with 2- or 4-picoline to yield the alcohol and then the unsaturated product (V-30) (*295,434*). The methyl group


(V-30)

in 3-ethyl-4-picoline reacts similarly (*435*). Improvements in procedure have been reported (*236,296*). *Cf.* Chapter XI (Table XI-6).

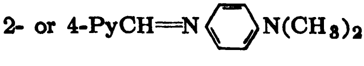
Similar condensation reactions have been found for ketones. Acetone reacts with 2-picoline to give 2-*i*-butenylpyridine (*297*). 2-Picoline and quinaldine have been reacted with a series of ketones such as ethyl oxomalonate, diphenyl triketone, ethyl benzoylglyoxylate, benzil, and alloxan to yield carbinols (*298*).

2-Picoline and acetic anhydride give V-31 (*299*). Ethyl chlorocarbonate reacts with 2- and 4-alkylpyridines to give compounds


(V-31)

formed from two molecules of the pyridine compound and one of the ester. It is believed that the second pyridine ring has been opened (*300*).

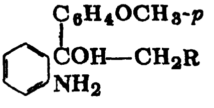
2- and 4-Picolines condense with *p*-nitrosodimethylaniline in the presence of piperidine to give V-32 (*436*). Quaternization of the


(V-32)

pyridine nucleus enables the reaction to be run at lower temperatures (*437*).

A few representative examples will be given of condensations of alkylpyridines with compounds such as ketones, esters, and nitriles in the presence of metals or metallic compounds. These condensations, considered as reactions of metallopyridine compounds, are treated more fully in Chapter VII.

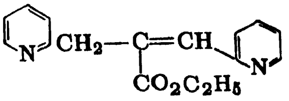
2-Amino-4′-methoxybenzophenone condenses with 2-picoline or 3-picoline to yield carbinols (V-33). 4-Picoline does not react in this case (*301*). 3-Picoline has been condensed with methyl esters in the presence of sodium amide to give 3-picolyl ketones (*64*). A similar condensation was obtained with 2-picoline in the presence of sodium amide or potassium amide (*302*). Quinaldine and lepidine reacted in the same manner (*303*).



R = 2-pyridyl
3-pyridyl

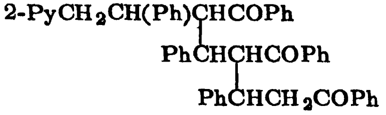
(V-33)

A Claisen condensation of 2-picoline and ethyl oxalate in the presence of sodium amide gave ethyl 3-(2-pyridyl)pyruvate which in turn underwent an aldol condensation with another molecule of 2-picoline to give ethyl 2-picolyl-3-pyridylacrylate (V-34) (*303*). Quinaldine also gave this reaction (*303*). (*Cf.* Chapter XI (Table XI-8).)

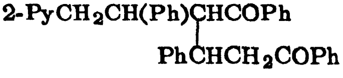


(V-34)

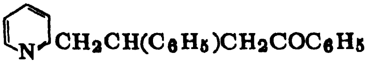
Michael condensations have been obtained with 2-picoline, quinaldine, and lepidine (*304*). Benzalacetophenone and 2-picoline in the presence of sodium amide give V-35 and V-36. These are formed by further condensation of benzalacetophenone with the initial product (V-37).


$$\begin{array}{l}\text{2-PyCH}_2\text{CH(Ph)CHCOPh} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\text{PhCHCHCOPh} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\quad\text{PhCHCH}_2\text{COPh}\end{array}$$

(V-36)


$$\begin{array}{l}\text{2-PyCH}_2\text{CH(Ph)CHCOPh} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\quad\text{PhCHCH}_2\text{COPh}\end{array}$$

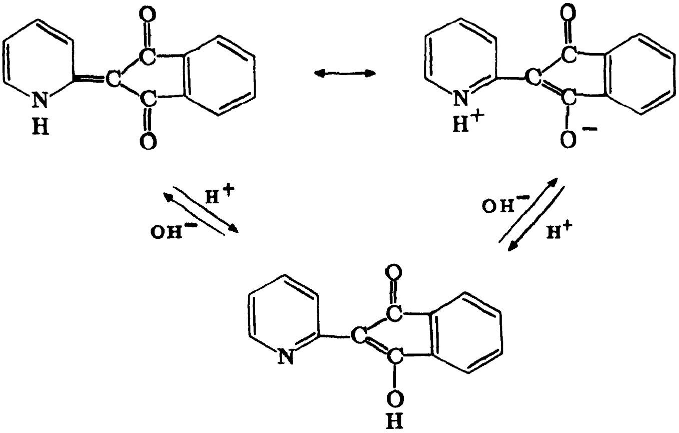
(V-35)



(V-37)

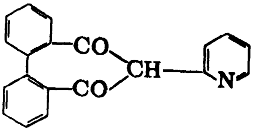
The application of the Mannich reaction to 2- and 4-picolines leads to 2- and 4-(β-aminoethyl)pyridines. Tseou obtained 2-(β-diethylaminoethyl)pyridine from 2-picoline, diethylamine, and formaldehyde (*305*). 4-Picoline and 2-ethylpyridine undergo this reaction but are less active than the quinolines. Frequently two molecules of the amine are added (*306*). The reaction has been applied to the synthesis of a number of amines (*307,308,309*) and sulfanilamides (*310*).

Phthalic anhydride condenses with 2- and 4-picolines and their quinoline analogs to yield colored compounds called pyrophthalones in the pyridine series and quinophthalones in the quinoline series. The reaction was discovered by Jacobsen and Reimer (*311*). The compounds may exist in isomeric forms and undergo structural changes with changes in hydrogen ion concentration. The structural possibilities have been critically presented by Mosher (*312*); and, based on the work of Kuhn and Bär (*313*), the most probable structural scheme is V-38. Naphthalic anhydride has been condensed with 2-picoline, 2,4-lutidine, 2-6-lutidine, and 2,4,6-collidine in the presence of zinc chloride to yield a series of 2-pyridonaphthalones (*314*). It was assumed that the higher homologs condensed at the 2-methyl group. Diphenic anhydride also has been condensed with the picolines and methylquinolines to give compounds with



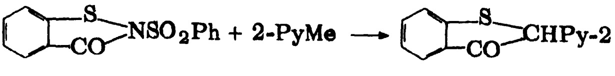
(V-38)

seven-membered rings (V-39). The reaction is more difficult with the pyridine compounds and a zinc chloride catalyst is required (*315*).



(V-39)

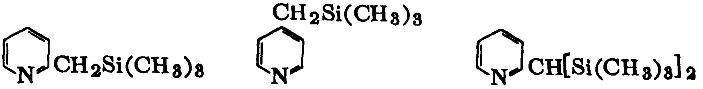
Benzenesulfonylbenzisothiazolone has been condensed with 2-picoline in the presence of glacial acetic acid to give V-40 (*431*). The reaction is given by compounds containing active methylene groups.



(V-40)

i. Side-Chain Metalation

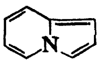
The introduction of alkali metals in the side chain and the synthetic value of the reaction have been discussed in the section on alkylation with organometallic compounds (p. 167). The finding of Brown and Murphey that the alkyl group in the 3 position may be metalated has been confirmed by others (*64,301,783–785*). Silicon has been introduced into the side chain by the action of chlorotrimethylsilane on 2- and 4-picolines in the presence of potassium amide, giving trimethylsilylmethylpyridines (V-41) (*316*). A similar reaction occurs with chlorotriethyltin (*695*).



(V-41)

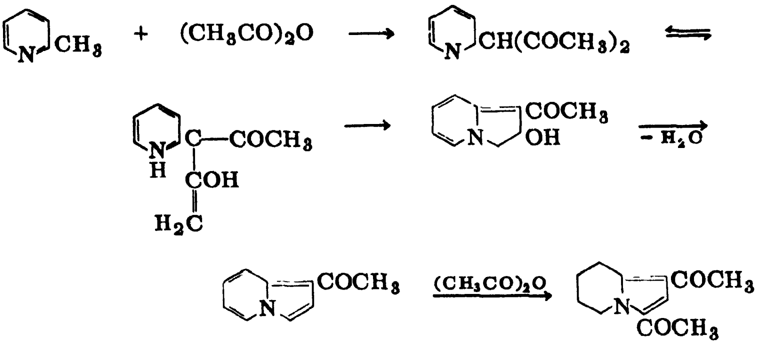
j. Synthesis of Condensed Ring Systems

2-Picoline and its dervatives condense with acid anhydrides or α-haloketones to yield pyrrocolines (V-42). Equations V-43 and V-44

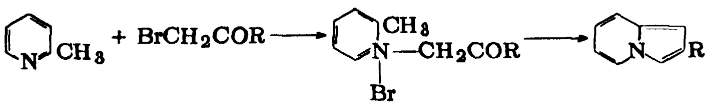


(V-42)

illustrate the reactions and possible mechanisms for the two classes of reactants (*318*).



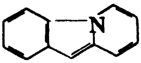
(V-43)



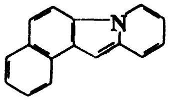
(V-44)

The synthesis of pyrrocolines has been reviewed by Borrows and Holland (*318*). 6-Phenyl-2-picoline and 2,4-lutidine react with anhydrides, but quinaldine does not. Anhydrides other than acetic and propionic do not react. Quinaldine does not react with α-haloketones to give a pyrrocoline. A number of 2-arylpyrrocolines have been obtained from substituted ω-bromoacetophenones and 2-picolines (*320*). Steric hindrance in the ketone prevents the reaction (*320*). 6-Ethylpyrrocoline was obtained from 5-ethyl-2-picoline and ethyl bromopyruvate (*342*). A series of pyrrocolines was obtained from the reactions of bromoacetone and 3-bromo-4-phenyl-2-butanone with 2-picoline and alkyl-2-picolines (*67*).

2-Benzyl and 2-(α-naphthylmethyl)pyridine cyclize on heating with copper at about 580–590°C. to yield V-45 and V-46, respectively (*88*). The analogous 4-substituted products do not give this reaction, which may thus be used to distinguish between 2- and 4-benzyl(or naphthylmethyl)pyridines (*88*).



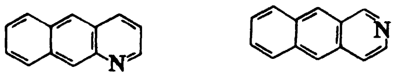
(V-45)



(V-46)

Although pyridine and its derivatives give pyrrocolines when condensed with acetylenedicarboxylic esters (*319*), 3-picoline failed to give this reaction (*321*). Isoquinoline gave a product which may be a pyrrocoline (*321*).

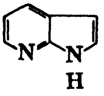
2- and 4-Xylylpyridines when heated with lead dioxide or copper at about 600°C. cyclize to yield α- and β-azanthracenes (V-47) (*87*). When the xylyl derivatives have been formed from substituted pyridines, the azanthracenes obtained have substituents on the nitrogen-containing ring.



α-Azanthracene **β-Azanthracene**

(V-47)

2-Formamido-3-picoline on heating in the presence of sodium anilide cyclizes to give 7-azaindole (V-48). 2-Formamido-3-ethylpyridine gives the 3-methyl derivative, and 2-acetamido-3-picoline the 2-methyl derivative of 7-azaindole (*322,335*).



(V-48)

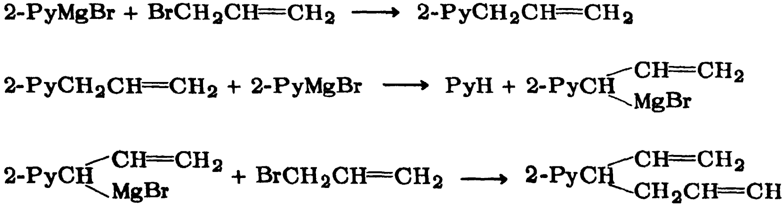
B. ALKENYL AND ARALKENYLPYRIDINES

1. Preparation

a. From Metallopyridine Compounds

Just as alkylpyridines are prepared from metallopyridine compounds and alkyl halides. alkenylpyridines are obtained by using unsaturated halides. Thus Chichibabin (*120*) converted 4- and 2-picolines to 4-(3-butenyl)pyridine and 2-(3-butenyl)pyridine, respectively, in the presence of sodium amide. The latter pyridine compound was also prepared in a 65% yield from 2-picolyllithium and allyl bromide (*440*). 2- and 4-Dodecenylpyridines have been similarly prepared (*356*). Longer reaction periods and higher temperatures are required for the longer chain alkenyls (*693*).

Pyridylmagnesium halides react in the same way. 3-Allylpyridine (*136*) and 3-methallylpyridine (*136,441*) were obtained from 3-pyridylmagnesium bromide and allyl bromide and methallyl chloride, respectively. The 3-allylpyridine was obtained in 79% yield. A higher boiling compound was obtained in the reaction of allyl bromide and 3-pyridylmagnesium bromide (*136*). This compound may be analogous to 2-(1-vinyl-3-butenyl)pyridine, which Troyanowsky (*440*) obtained along with 2-allylpyridine by the reaction of allyl bromide with 2-pyridylmagnesium bromide (V-49). 2-Allylpyridine was obtained in 50% yield, and when a large excess of allyl bromide was used, 2-(1-vinyl-3-butenyl)pyridine was also obtained in 50% yield.



$$\text{2-PyMgBr} + \text{BrCH}_2\text{CH}{=}\text{CH}_2 \longrightarrow \text{2-PyCH}_2\text{CH}{=}\text{CH}_2$$

$$\text{2-PyCH}_2\text{CH}{=}\text{CH}_2 + \text{2-PyMgBr} \longrightarrow \text{PyH} + \text{2-PyCH}\begin{cases}\text{CH}{=}\text{CH}_2\\ \text{MgBr}\end{cases} \qquad \text{(V-49)}$$

$$\text{2-PyCH}\begin{cases}\text{CH}{=}\text{CH}_2\\ \text{MgBr}\end{cases} + \text{BrCH}_2\text{CH}{=}\text{CH}_2 \longrightarrow \text{2-PyCH}\begin{cases}\text{CH}{=}\text{CH}_2\\ \text{CH}_2\text{CH}{=}\text{CH}_2\end{cases}$$

The condensation of picoline with dienes in the presence of sodium to yield alkenylpyridines (*179*) is discussed on p. 191.

b. Condensation with Carbonyl Compounds

The condensation of aldehydes and ketones with 2- and 4-alkylpyridines containing two alpha hydrogens to yield alkenyl derivatives has been mentioned (p. 192). Although the first step is the formation of an alcohol, the reaction can be made to go in one step under dehydrating conditions.

By using high temperatures it was possible to condense cinnamaldehyde with 2-picoline to give 2-(4-phenyl-1,3-butadienyl)pyridine. 4-Picoline did not react as readily and gave the alcohol instead (*285*).

Zinc chloride has been widely used as a dehydrating agent, for example, in the preparation of stilbazoles (*105,283,442,444*), 6-propenyl-2,4-lutidine (*445*), and 2-(2-methylpropenyl)pyridine (*297*). 1,2-Bis(4-pyridyl)ethylene has been prepared in 13% yield by the reaction of isonicotinaldehyde with 4-picoline in the presence of zinc chloride (*76*). The same compound was obtained as one of the products in the reaction between sulfur and 4-picoline (*76*).

In connection with the reaction of 2,6-lutidine and benzaldehyde it may be interesting to note that the product to which Ladenburg (*446*) assigned the 1,2-diphenyl-3-(2-pyridyl)cyclopropane structure is actually 2,6-distyrylpyridine (*282*).

Although zinc chloride has been useful in this reaction, acetic anhydride gives better results (*279*); it requires lower temperatures and is more convenient on a large scale (*447*).

Using acetic anhydride as a condensing agent, Phillips (*448*) studied the reaction of 2- and 4-ethylpyridines with benzaldehydes. 4-Ethylpyridine gave yields of 60 and 65%, respectively, with *p*-dimethylaminobenzaldehyde and *p*-anisaldehyde. 2-Ethylpyridine gave yields of about 5 and 0% with the same compounds. This is opposite to the order of reactivity reported for the 2- and 4-picolines. Benzaldehyde and *m*-nitrobenzaldehyde gave 70% yields with 2-ethylpyridine and 80% with 4-ethylpyridine. *p*-Nitrobenzaldehyde gave 90% yields with both pyridine derivatives.

o-Hydroxybenzaldehyde gave respective yields of 68 and 70% when condensed with 2- and 4-picolines; *p*-hydroxybenzaldehyde gave yields of 78 and 57% for the same pyridine compounds (*449*). *p*-Chlorobenzaldehyde gave yields of 55 and 63%, respectively, in condensations with 2- and 4-picolines in the presence of acetic anhydride (*447*).

2,6-Lutidine reacts stepwise to yield 6-methyl-2-stilbazoles and 2,6-distyrylpyridines (*118,449*); the more reactive aldehydes such as *p*-nitro- and *p*-cyanobenzaldehydes tend to form the distyryl derivative (*118*), while the less active such as 4-acetoxy-3,5-diiodobenzaldehyde (*449*) and *p*-hydroxybenzaldehyde (*118*) form the mono.

Acetic anhydride has also been used in the preparation of 5-ethyl-2-stilbazole (*451*), 5-butyl-2-stilbazole (*20*), 4,5-diethyl-2-stilbazole (*458*), 5-hexyl-2-stilbazole (*20*), Bz-nitro-3-methyl-2-stilbazoles (*278*), 2,4- and 2,6-distyrylpyridines (*452*), 6-*i*-propyl-3-methyl-2-stilbazole (*453*), and a series of 1-phenyl-1-(2- or 4-pyridyl)-2-arylethylenes from 2- or 4-benzylpyridines and aromatic aldehydes (*450*).

Alkyl groups in the 4 position on the pyridine ring do not react as rapidly as methyl groups in the 2 and 6 positions. 4-Propyl-2,6-lutidine and benzaldehyde gave a mixture of mono- and distyryl derivatives (*454*). A similar result was obtained with 4-ethyl-2,6-lutidine. 4-Ethyl-6-(β-hydroxyphenethyl)-2-picoline was also indicated. Zinc chloride was the condensing agent (*444*).

6-Acetamido-2-picoline and 2-acetamido-4-picoline reacted with benzaldehyde in the presence of acetic anhydride to give low yields (ca. 12%) of the stilbazole (*457*). 1,6-Dimethyl-2(1*H*)-pyridone and *m*-nitrobenzaldehyde under similar conditions gave only a 1% yield of the stilbazole (*457*).

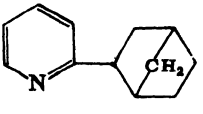
Other groups on the pyridine ring do not appear to interfere with the reaction. 3-Nitro-4-picoline condensed with benzaldehyde in the presence of piperidine to give 3-nitro-4-stilbazole (*455*), and 3-nitro-2,4,6-collidine gave what is probably 4,6-dimethyl-5-nitro-2-stilbazole (*203*). 5-Ethoxy-2-picoline condensed with benzaldehyde in the presence of zinc chloride to give a 40% yield of the stilbazole (*109*) and 6-methylnicotinic acid reacted by heating at 170–180° (*456*). In the reaction of 4,6-dichloro-2-picoline with benzaldehyde in the presence of zinc chloride, one chlorine was replaced by hydroxyl to give what may be either 4-chloro-6-hydroxy-2-stilbazole or 6-chloro-4-hydroxy-2-stilbazole (*443*). However, when a cyano group was present on the ring as in 5-cyano-4,6-dichloro-2-picoline, the condensation occurred without replacement of a chloro group.

c. Condensation with Dienes

The condensation of 2-picoline with dienes yields alkenyl derivatives, as discussed above (p. 191). A mixture of a 30–40% yield of 2-(3-pentenyl)pyridine and 30% yield of 2-[1-(2-butenyl)-3-pentenyl]-pyridine was obtained when 2-picoline and butadiene were condensed in the presence of sodium (*179*).

2-Vinylpyridine, like styrene, condenses with dienes (*461*). Using this reaction, Doering and Rhoads obtained 2-(3-cyclohexenyl)pyridine and 2-(3,4-dimethyl-3-cyclohexenyl)pyridine from 2-vinylpyridine and 1,3-butadiene and 2,3-dimethyl-1,3-butadiene, respectively (*459*).

The reaction has been applied to a large number of dienes by Petrov and Ludwig (*460*). The expected diene adducts were given by 1,3-pentadiene, isoprene, 2,4-hexadiene, 2,3-dimethyl-1,3-butadiene, cyclohexadiene, and cyclopentadiene. The last compound gave V-50. The highest yield was 60% for the reaction with 2,3-dimethyl-1,3-butadiene. The structures of the adducts have been determined by dehydrogenation to known arylpyridines (*459–461*).



(V-50)

d. Dehydration of Carbinols

The ready availability of carbinols, especially from the reaction of formaldehyde with 2- and 4-picolines, makes them useful for the synthesis of alkenes by dehydration. This can be accomplished by heating alone or in the presence of acidic or alkaline reagents.

2-Vinylpyridine has been prepared by the direct distillation of 2-pyridineethanol (*462*), but this method has little practical value, since catalysts reduce both duration and intensity of heating.

Among the acidic catalysts, phosphorus pentoxide has been used in the preparation of 3,5-dimethyl-2-propenylpyridine (*24*), 3-heptenylpyridine (*136*), and 3-vinylpyridine (*469*). Sulfuric acid has been used in the preparation of 2-*i*-propenylpyridine (*463,465*), 2-cyclohexenylpyridine (*464*), stilbazoles (*260,532*), and a series of 2- and 4-(cyclopentenyl)- and 2- and 4-(cyclohexenyl)pyridines (*470*). Phosphoric acid (*466*), potassium bisulfate (*526*), and boron trifluoride (*468*) have also been employed. Cupric sulfate gave an 80% yield of 1,2-bis(2-pyridyl)ethylene from 1,2-bis(2-pyridyl)ethanol (*33*).

To prevent polymerization of the alkenylpyridine during the course of the reaction, *t*-butylcatechol has been used as an inhibitor (*466,468*).

Potassium hydroxide was used by Ladenburg (*462*) to prepare 2-vinylpyridine, and has found wide application since, *e.g.*, in the preparation of 2,4-dimethyl-6-vinylpyridine (*292*), 4-vinylpyridine (*471*), 2-vinylpyridne (*294,460*), 5-ethyl-2-vinylpyridine (*472*), 2,4-divinylpyridine (*473*), 2,6-divinylpyridine (*473,474*), and 6-vinyl-2-picoline (*474*). Polymerization is reduced by running the reaction under low pressure so that the 2-vinylpyridine distills as rapidly as it forms (*475*). Isolation of the carbinol may be avoided by direct addition of alkali to the reaction mixture of the pyridine compound and formaldehyde (*476*).

Aluminum oxide has been used as a catalyst in the vapor phase dehydration of 2-pyridineethanol at 330°C.; the yield is 84% after two passes over the catalyst. Polymer formation is inhibited by shortened contact time (*447*).

A comparison of the various methods for the preparation of 2-vinylpyridine shows the following percentage yields: distillation over potassium hydroxide, 80%; heating with sulfuric acid at 170°C., 65%; heating with potassium bisulfate and hydroquinone, 76%; and heating with potassium hydroxide and hydroquinone, 91%. The hydroquinone was used as polymerization inhibitor (*294*).

e. Side-Chain Dehydrohalogenation and Dehalogenation

Since halo compounds are usually obtained from alcohols or alkenes, these methods have limited value in preparing alkenes, but they are of greater use in the preparation of alkynyl derivatives. Alkaline conditions are generally used.

Alcoholic potassium hydroxide has been used in the preparation of 3-vinylpyridine (*469*), 3-vinyl-4-picoline (*480*), 4′-methyl-2-stilbazole (*524*), and 2,6-dichloro-3-vinyl-4-picoline (*478*) from the corresponding chloro derivatives. The latter compound was also obtained by treatment of the chloro compound with silver oxide (*478*).

Amines have been used as alkaline agents in the dehydrohalogenations. Triethylamine has been used in an improved synthesis of 3-vinylpyridine from 3-(α-chloroethyl)pyridine (*479*). By treating the chloro compound with triethylamine for ten hours at 80°C. and then refluxing in potassium hydroxide solution, a 65% yield of 3-vinylpyridine was obtained (*459*). 1-(2-Pyridyl)-2-(3-pyridyl)ethylene has been obtained by treating the bromoethane derivative with cyclohexylamine and sodium bicarbonate (*430*).

Although sodium amide is not generally used, 4-[1-(3-butenyl)-4-pentenyl]pyridine was obtained in an alkylation of 4-picoline with 1,4-dichlorobutane in the presence of sodium amide (*42*).

In the electrolytic reduction of 2-(2-hydroxy-3,3,3-trichloropropyl)pyridine, a small amount of 2-propenylpyridine was obtained. This was probably due to a combination of dehydration and dehydrohalogenation (*480*).

f. Side-Chain Dehydrogenation

The increasing availability of ethylpyridines such as 5-ethyl-2-picoline has led to the increasing use of catalytic vapor-phase dehydrogenation for the preparation of vinylpyridines. Since conversions are not high, separation of the unreacted compound from the vinylpyridine is necessary before recycling. These separations are discussed on p. 207.

Hays (*481*) used oxides of the metals of groups IV, V, and VI at temperatures of 450–800°C. The products were isolated by freezing at –30 to –70°C. in a low-boiling hydrocarbon solvent.

A mixture of iodine, oxygen, and pyridine compound substituted by an ethyl or *i*-propyl group, was heated at 450–800°C. to dehydrogenate the alkyl group (*482*). The oxygen can be diluted with either nitrogen or water vapor. The conversions are about 40% and the yields about 80%.

2- and 4-Ethylpyridines have been converted to 2- and 4-vinylpyridines at 650–750°C. using either silica, tungstic acid, or ceric oxide as catalysts (*483*). The pyridine compound was first mixed with carbon dioxide. The yields were high (75–90%) but no data are given for percentage conversion. Other metal oxides of groups IV, V, and VI are also useful as catalysts. In a similar way 5-vinyl-2-picoline was obtained from 5-ethyl-2-picoline (*484*).

Peroxides such as cumene hydroperoxide and di-*t*-butyl peroxide have also been used as catalysts (*485*).

Chromic oxide catalyst has been used at temperatures of 425–650°C. in the dehydrogenation of 2- and 4-alkylpyridine homologs from ethyl to amyl. Sulfur was used as a polymerization inhibitor (*486*).

Dealkylation occurs during these processes. Pyridine, 2-picoline, 3-picoline, 2,5-lutidine, and 3-vinylpyridine have been obtained in the dehydrogenation of 5-ethyl-2-picoline to 5-vinyl-2-picoline (*487*).

2. Properties

The alkenylpyridines are liquids possessing higher boiling points and greater densities than the corresponding alkyl derivatives. The aralkenyl derivatives are solids at room temperature and have very high boiling points. The physical properties of the alkenylpyridines are summarized in Table V-8, the cycloalkenylpyridines in Table V-9, and the aralkenylpyridines in Table V-10 (pp. 251 ff.).

Like the alkyl derivatives, the alkenyl compounds form complexes with inorganic salts and salts with organic and inorganic acids. Unlike the picolines and lutidines, 2- and 4-vinylpyridines fail to complex with chromium(VI) oxide because of rapid oxidation (*160*). A 1 : 1 complex of 2-vinylpyridine and copper(II) chloride has been isolated. Its properties indicate that both the nitrogen atom and the double bond are attached to the copper atom (*488*).

Stilbazoles, like aralkylpyridines, nitrate in the benzene ring. The pyridine ring is not affected (*317, 498*). Although the usual quaternization reactions are given, 5-ethyl-2-vinylpyridine upon heating with methyl iodide at 300°C. for two hours yielded a base, $C_{10}H_{13}N$, of unknown structure. The compound did not appear to be unsaturated (*543*). 2-Vinylpyridine and pyridine hydrochloride react to give a quaternary salt of pyridine and 2-(β-chloroethyl)pyridine (*544*).

Some lack of consistency in the melting points and solubilities of stilbazoles has been attributed to possible geometrical isomerism. The lower melting forms were considered to be *cis*. However, Royer (*489*) was unable to prepare any of the low melting forms following published procedures (*490*). *o*-Nitrostilbazole has been separated into *cis* and *trans* forms by fractional crystallization (*491*). Attempts have been made to prepare substituted *cis* and *trans* stilbazoles and stilbazolium salts from 2- or 4-picoline or 2- or 4-picolinium salts. The *trans* form was always obtained except in the case of *o*-hydroxybenzaldehyde, which yielded a *cis* compound when condensed with 2- and 4-picolines in the presence of acetic anhydride and then quaternized with methyl iodide, and a *trans* compound when condensed with 2- and 4-picoline methiodides. The *o*-hydroxy group stabilizes the *cis* configuration. Acetylation converts the *cis* to the *trans* form. *p*-Hydroxyl groups do not possess this stabilizing effect (*492*).

Ultraviolet absorption spectra have been reported for 2-stilbazole, 4-stilbazole, 2,4-distyrylpyridine, 2,6-distyrylpyridine, 2,4,6-tristyrylpyridine, and various substituted stilbazoles and pyridine dienes. Comparisons were made with analogous phenyl derivatives (*493*). *trans*-Stilbazoles absorb at longer wavelengths in the ultraviolet (*492*). Ultraviolet spectra have also been reported for 5-methyl-2-vinylpyridine (*440*) and 4-vinylpyridine (*353*). Raman spectra have been determined for 2-allylpyridine and related compounds (*440*).

2-Stilbazole and analogs obtained from the condensation of furfuraldehyde, cinnamaldehyde, and geranial with 2-picoline possess some insecticidal activity (*494*).

Fractional distillation has been used to separate alkenylpyridines from their saturated analogs, for example, 2-ethylpyridine from 2-vinylpyridine (*483*) and 5-ethyl-2-picoline from 6-methyl-3-vinylpyridine (*482*). Fractional crystallization has also been used (*481,495*).

Since alkylpyridines are stronger bases than the alkenyl derivatives, separation has been achieved by controled acidification in aqueous media, the alkenyl compound remaining insoluble (*496,497*). Base strengths of monovinylpyridines have been reported (*781*).

Alkenylpyridines may also be separated by polymerization (p. 212); the alkyl derivatives cannot, of course, polymerize (*485*).

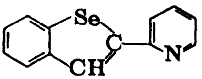
3. Reactions

a. Oxidation

The olefinic double bond is readily cleaved by strong oxidizing agents, as in the potassium permanganate oxidation of 4,6-dimethyl-5-nitro-2-stilbazole to 4,6-dimethyl-5-nitropicolinic acid (*203,292*) or the nitric acid oxidation of 4′-methyl-3′-nitro-2-stilbazole to picolinic and 4-methyl-3-nitrobenzoic acids (*498*).

Ozonolysis yields aldehydes and acids. 2-Stilbazole gave picolinaldehyde, (*499*), while 4-stilbazole gave a mixture of aldehydes and acids, isonicotinaldehyde being obtained in 20% yield (*500*). However, Kaslow and Stayner could only obtain the acids upon the ozonolysis of 2- and 4-stilbazoles and their 3′-nitro derivatives (*501*). Similarly 6-*i*-propyl-3-methylpicolinic acid was obtained from 6-*i*-propyl-3-methyl-2-stilbazole (*453*).

2-Stilbazole has been oxidized with selenium dioxide to the diketone. 2-(2-Pyridyl)selenonaphthene (V-51) was obtained as a by-product (*502*). 4-Stilbazole gave only the selenonaphthene derivative.



(V-51)

b. Reduction and Hydrogenation

Reduction studies have primarily concerned the stilbazoles and their derivatives. Over Raney nickel under mild conditions, the double bond may be reduced selectively, with retention of nuclear iodine (*449*) or reduction of nuclear nitro to amino groups (*489*). Under more vigorous conditions, reduction of the double bond and pyridine ring occur to give piperidylethyl derivatives (*452*). Sodium and ethanol also reduce both pyridine ring and alkene linkage (*72*).

Palladium catalyst has been used in the hydrogenation of 2-propenyl-3,5-lutidine to the propyl derivative (*24*) and of various stilbazoles to the dihydro derivatives (*505*). 2-Cyclopentylpyridine has been obtained by reduction of 2-cyclopentenylpyridine over platinum oxide (*504*).

Phosphorus and iodine reduce only the double bond in 2′-nitro-2-stilbazole (*506*).

c. Addition of Inorganic Molecules

As would be expected, bromine and chlorine add across the double bond of the stilbazoles to yield α,β-dibromophenethylpyridines (*447,503,507–509*) and the corresponding α,β-dichloro compounds (*509*). Some compounds first formed *N*-perbromides, which on heating rearranged to give the dibromo derivative (*447*). A temperature of 117°C. was required to rearrange the perbromide of 4-stilbazole, which lost hydrogen bromide to yield a monobromostilbazole (V-52) (*447*).

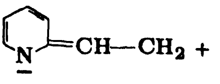
$$\text{4-Py—CH}{=}\text{CBr—Ph or 4-Py—CBr}{=}\text{CH—Ph}$$

(V-52)

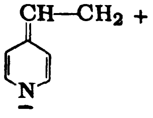
Although 2-stilbazole is reported to form a hydrogen chloride addition product during ozonolysis in dilute hydrochloric acid (*499*), Räth was unable to obtain an addition compound of hydrogen bromide (*510*). Apparently the monobromo derivative of the phenethylpyridine is not stable and loses hydrogen bromide to give the stilbazole. This has been confirmed by Blood and Shaw, who obtained stilbazoles by the action of only one equivalent of alkali on the α,β-dibromo- or dichlorophenethylpyridine derivatives (*509*).

Hydrazoic acid reacts with 2-vinylpyridine to yield 2-(β-azidoethyl)pyridine in 97% yield (*511,512*).

Sodium bisulfite reacted with 2- and 4-vinylpyridines, but not 3-vinylpyridine, to yield the corresponding pyridineethanesulfonic acids. This has been attributed to the resonance forms V-53 and V-54, which facilitate nucleophilic attack (*479*).



(V-53)



(V-54)

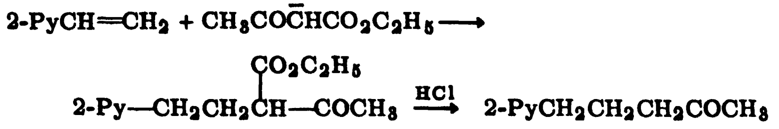
d. Addition of Organic Molecules

The electrophilic character of 2- and 4-vinylpyridines serves to explain their reactions with a large variety of organic compounds. These reactions were studied by Doering and Weil (*479*), who showed that 2-vinylpyridine adds sodiomalonic ester (V-55) and sodioacetoacetic ester (V-56). Hydrogen cyanide, ethanol, and amines such as

$$\text{2-PyCH}{=}\text{CH}_2 \; + \; \overset{-}{\text{C}}\text{H(CO}_2\text{C}_2\text{H}_5)_2 \longrightarrow$$

$$\text{2-PyCH}_2\text{CH}_2\text{CH(CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow{\text{NaOH}} \text{2-PyCH}_2\text{CH}_2\text{CH(CO}_2\text{H)}_2 \xrightarrow{\Delta}$$

$$\text{2-PyCH}_2\text{CH}_2\text{CO}_2\text{H} \qquad \text{(V-55)}$$



$$2\text{-PyCH=CH}_2 + \text{CH}_3\text{CO}\overset{-}{\text{C}}\text{HCO}_2\text{C}_2\text{H}_5 \longrightarrow 2\text{-Py—CH}_2\text{CH}_2\overset{\text{CO}_2\text{C}_2\text{H}_5}{\text{CH}}\text{—COCH}_3 \xrightarrow{\text{HCl}} 2\text{-PyCH}_2\text{CH}_2\text{CH}_2\text{COCH}_3$$

(V-56)

diethylamine and piperidine also add. In all cases the mode of addition results in the 1,2-disubstituted ethane of the type $\text{PyCH}_2\text{CH}_2\text{R}$.

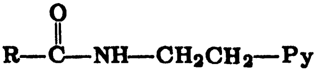
The Michael reaction of ketones and esters with 2-vinylpyridine has been further investigated by Boekelheide's group (*513–515*), Levine's group (*178,516*), and Albertson (*518*). Although the work of Doering and Weil (*479*) indicated that basic catalysts are needed for the reaction, Boekelheide and Rothchild (*514*) found that addition of ethyl acetoacetate could be accomplished in the presence of an acidic catalyst such as dry hydrogen chloride. Triton B was also effective (*178*). A simple ester, ethyl *i*-butyrate, was likewise condensed with 2-vinylpyridine. Depending upon molecular proportions of reactants, mono- or dipyridylethylation may occur (*178*). A Michael reaction has been carried out with 2-*i*-propenylpyridine and propiophenone (*526*).

Nitriles such as phenylacetonitrile (*520*), ethyl cyanoacetate (*520*), and ethyl acetamidocyanoacetate (*521*) give the expected reactions with 2-vinylpyridines. Even such a simple nitrile as propionitrile adds two molecules of 2-vinylpyridine (*178*).

The Michael reaction of 2- and 4-vinylpyridines with 2- and 4-picolines has been discussed (p. 191).

The pyridylethylation by 2- and 4-vinylpyridines of amines has been further investigated (*307,517,527,776*). Primary amines give lower yields than secondary but not because of differences in basicity. Steric factors enter into the reactions with secondary amines. Although acidic catalysts are useful (*528*), basic catalysts are required with weakly basic amines such as pyrrole (*307*). Aniline was pyridylethylated using acetic acid as a catalyst (*517,522*). Sodium was not a good catalyst in this reaction (*527*). Bispyridylethylation can occur with primary amines (*776*).

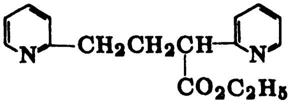
2- and 4-Vinylpyridines, as well as 6-methyl-3-vinylpyridine, react with amides to give V-57 (*527*). This is an instance where the 3-vinyl group reacts.



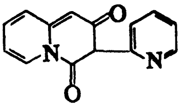
$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH-CH_2CH_2-Py$$

(V-57)

The condensation of 2-vinylpyridine and ethyl 2-pyridineacetate gives the expected ethyl α,γ-bis(2-pyridyl)butyrate (V-58) and also a cyclic compound (V-59), which is probably formed by the condensation of two molecules of ethyl 2-pyridineacetate (*523*).



(V-58)



(V-59)

2-Vinylpyridine, like *p*-nitrostyrene, undergoes a Meerwein reaction with benzenediazonium chloride and 1-chloro-1-(2-pyridyl)-2-phenylethane is formed (*524*). Ethyl diazoacetate condensed with 2-vinylpyridine to yield 2-(2-pyridyl)cyclopropanecarboxylic acid (*525*).

For further reactions of vinylpyridines with esters, see Chapter XI (Table XI-9).

e. Willgerodt Reaction

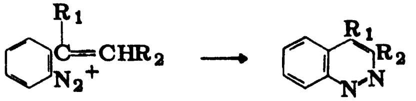
2- and 4-Vinylpyridines undergo the Willgerodt reaction with ammonium polysulfide to yield 1-pyridineacetamide (*530*) and 4-pyridineacetamide (*531*). The latter compound was used as a starting point in the synthesis of a 4-pyridyl analog of papaverine.

f. Diels-Alder Reaction

The Diels-Alder reaction has been discussed in the section dealing with the preparation of cyclohexenylpyridines (p. 202). It is interesting to note that 3-vinylpyridine behaves similarly to 2-vinylpyridine in this reaction (*459*).

g. Synthesis of Cinnolines

The Widman-Stoermer synthesis of cinnolines (V-60) is applicable where R_1 or R_2 are pyridyl radicals (*260,532*). The reaction


(V-60)

is favored by R_1 = *p*-methoxyphenyl; with other phenyl radicals the yields decrease rapidly with increasing pH.

h. Polymers and Their Properties

In 1925 (*533*) it was shown that illumination causes 5-cyano-4,6-dichloro-2-stilbazole to dimerize, apparently at the ethylenic double bond (*443*).

The need for synthetic rubber during World War II gave strong impetus to the study of the polymerization and copolymerization of vinylpyridines. Polyvinylpyridines have similar properties to polystyrenes, but require a higher temperature for molding; the presence of the tertiary nitrogen makes them a convenient starting point for the preparation of cationic polyelectrolytes (*534*).

Although poly-4-vinylpyridine is soluble in solvents such as alcohols, acetone, and dioxane, even when diluted with water, crosslinking with ethylene dibromide yielded insoluble polymers (*534*).

The electrical properties of poly-2-vinylpyridine have been reported, including transference numbeis, equivalent weight, and degree of ionization (*535*). The polar properties of poly-4-vinylpyridine picrate have also been reported (*536*).

Crosslinked polymers useful as ion exchange resins have been prepared by suspension polymerization of 2-vinylpyridine and 2,4-divinylpyridine. 2-Vinylquinoline may be used in place of 2-vinylpyridine. The homopolymeric *N*-alkyldivinylpyridinium hydroxides may be reduced to the piperidinium compounds (*473*).

Copolymerization of vinylpyridine with styrene serves to reduce the charge density of the polymer (*534*). Methacrylic acid and 2-vinylpyridine give amphoteric copolymers. The properties of the copolymers were changed by changing the ratios of the monomers. The properties resembled those of polyvinylpyridine in acid solution and of polymethacrylic acid in basic solution (*537*).

The copolymerization of vinylpyridines and dienes has been used in the preparation of synthetic elastomers. After vulcanization the compounds have a high modulus and high tensile strength compared to the GR-S polymers. The flexing-hysteresis balance is usually superior for the vinylpyridine-diene copolymers (*538*).

Butadiene-vinylpyridine copolymers have excellent tensile strength but mill poorly. Since dichlorostyrene-butadiene copolymers are easily milled, dichlorovinylpyridine has been used in the copolymerization. The effect was not as great as desired. 2-*i*-Propenylpyridine did not copolymerize with butadiene (*465*).

Terpolymers of butadiene, styrene, and vinylpyridine show superior quality and equivalent processing to GR-S polymers. Notable improvements were shown in tensile strength, rebound, aging, cure stability, and crack resistance. Hysteresis temperature rise is adversely affected. Terpolymers are recommended where improved crack resistance and good aging properties are of prime importance (*539*).

Vinylpyridine copolymers may be dyed with acid dyestuffs. This is an important advantage over the styrene copolymers (*540*,*541*).

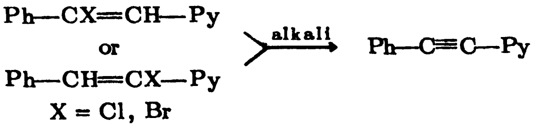
Ultraviolet absorption data are available for a number of vinylpyridine polymers and copolymers with butadiene (*542*).

C. ALKYNYL- AND ARALKYNYLPYRIDINES

1. Preparation

Aralkynylpyridines are most often prepared by the dehydrohalogenation of α,β-dihalophenethylpyridines (V-61) or α- or β-halostilbazoles (V-62). 2- and 4-Tolazoles (*447*), 6-methyl-2-tolazole (*545*), and 2,6-di(phenylethynyl)pyridine (*507*) have been prepared by the dehydrobromination of α,β-dibromophenethylpyridine derivatives with alcoholic potassium hydroxide. 2′-Nitro-2-tolazole (*546*,

$$\underset{X\,=\,\mathrm{Cl,\ Br}}{\mathrm{Ph{-}CHX{-}CHX{-}Py}} \xrightarrow{\text{alkali}} \mathrm{Ph{-}C{\equiv}C{-}Py} \qquad \text{(V-61)}$$

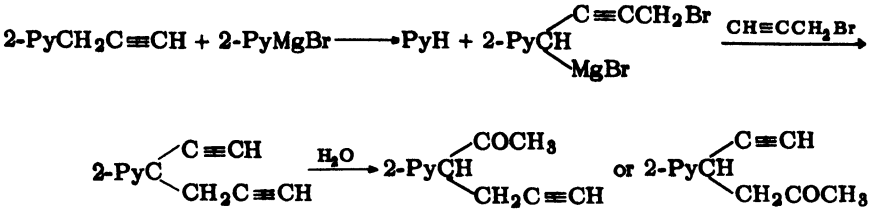


$$\left.\begin{array}{c}\mathrm{Ph{-}CX{=}CH{-}Py}\\ \text{or}\\ \mathrm{Ph{-}CH{=}CX{-}Py}\\ X = \mathrm{Cl,\ Br}\end{array}\right\rangle \xrightarrow{\text{alkali}} \mathrm{Ph{-}C{\equiv}C{-}Py} \qquad \text{(V-62)}$$

547) and 2′-nitro-5′-chloro-2-tolazole (*546*) have been prepared by similar treatment of the dichloro derivative. 2-Tolazole (*447*) and 2′-nitro-2-tolazole (*547*) have been prepared from the halostilbazoles. 3-Ethynylpyridine has been similarly prepared from 3-(α-chlorovinyl)pyridine (*467*).

Certain alkynylpyridines have been prepared from organometallic derivatives. For example, 2-picolyllithium and propargyl bromide give 2-(3-butynyl)pyridine along with a nearly equal amount of the isomeric allene, 2-(2,3-butadienyl)pyridine (*440*). 2-Pyridylmagnesium bromide reacts with two moles of propargyl bromide; the product hydrates to the acetylenic ketone V-63 or V-64 (*440*).

$$\text{2-PyMgBr} + \text{CH}{\equiv}\text{CCH}_2\text{Br} \longrightarrow \text{2-PyCH}_2\text{C}{\equiv}\text{CH}$$



$$\text{2-PyCH}_2\text{C}{\equiv}\text{CH} + \text{2-PyMgBr} \longrightarrow \text{PyH} + \text{2-PyCH}\begin{cases}\text{C}{\equiv}\text{CCH}_2\text{Br}\\ \text{MgBr}\end{cases} \xrightarrow{\text{CH}{\equiv}\text{CCH}_2\text{Br}}$$

$$\text{2-PyC}\begin{cases}\text{C}{\equiv}\text{CH}\\ \text{CH}_2\text{C}{\equiv}\text{CH}\end{cases} \xrightarrow{\text{H}_2\text{O}} \text{2-PyCH}\begin{cases}\text{COCH}_3\\ \text{CH}_2\text{C}{\equiv}\text{CH}\end{cases} \text{ or } \text{2-PyCH}\begin{cases}\text{C}{\equiv}\text{CH}\\ \text{CH}_2\text{COCH}_3\end{cases}$$

(V-63) (V-64)

Physical properties of the alkynylpyridines and aralkynylpyridines are summarized in Table V-11 (p. 262).

2. Reactions

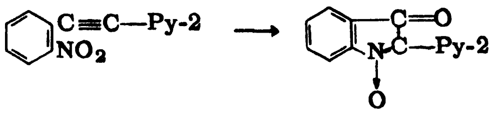
Like 2-stilbazole and 2-phenethylpyridine, 2-tolazole has been found to nitrate in the *o*-position of the benzene ring (*317*). The other known reactions of pyridylacetylenes all involve some form of attack at the triple bond. For example, 2,6-di(phenylethynyl)pyridine can be hydrogenated to 2,6-distyrylpyridine over a palladium catalyst (*507*). By hydration of the triple bond in the presence of sulfuric acid, 2-phenacylpyridine (V-65) (*447*), 2,6-diphenacylpyri-

$$\text{2-PyC}{\equiv}\text{CPh} \xrightarrow[\text{H}_2\text{SO}_4]{\text{H}_2\text{O}} \text{2-PyCH}_2\text{COPh}$$

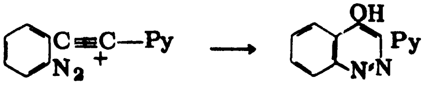
(V-65)

dine (*507*), and 2- and 4-(*p*-chlorophenacyl)pyridines (*548*) have been obtained. The formation of the acetylenic ketone V-63 or V-64 has been discussed above.

Certain *o*-substituents enter into cyclization reactions through the triple bond. Illumination or treatment with nitrosobenzene converts 2′-nitro-2-tolazole to 2-(2-pyridyl)isatogen (V-66) (*547*), while 2′-aminotolazoles undergo the Richter 4-hydroxycinnoline synthesis (V-67) (*546*).



(V-66)



(V-67)

D. DI- AND POLYPYRIDYLALKANES AND ALKENES

Alkanes substituted by more than one pyridyl radical are most often prepared by organometallic reactions (p. 167). A series of polymethylenebipyridines were prepared from 2-picolyllithium and 4-picolylpotassium with polymethylene dibromides (*111*). 2-Picolylsodium has also been used in this reaction (*110*). 2,2′-Methylenedipyridine has been obtained from 2-picolyllithium and either pyridine or 2-bromopyridine (*147*). The reaction with pyridine is best run in excess pyridine and a yield of 36.8% was obtained. In the reaction with 2-bromopyridine 2,2,′2″-methylidynetripyridine was also formed. 1,1-Bis(2-pyridyl)propane has been obtained by the reaction of bis(2-pyridyl)methyllithium and ethyl bromide (*148*), and 1,2-bis(2-pyridyl)ethane from 2-picolyllithium and 2-picolyl bromide (*114*).

The condensations of 2- and 4-vinylpyridines with 2- and 4-picolines in the presence of sodium have been discussed (p. 191). 2,2′- and 4,4′-Trimethylenebipyridine have thus been obtained (*519, 111*).

Bis(2-pyridyl)methane has also been obtained by the reduction of chlorobis(2-pyridyl)methane (*33*).

4,4′-Tetramethylenebipyridine has been obtained as a by-product from the reaction of 4-vinylpyridine and acetamide (*527*). From the reaction of sulfur with 4-picoline 1,2-bis(4-pyridyl)ethane, 1,2-bis(4-pyridyl)ethylene, and 1,2,3-tris(4-pyridyl)propane were obtained. 1,2,3,4-Tetrakis(4-pyridyl)butane was obtained by reduction of 2,3,4,5-tetrakis(4-pyridyl)thiophene. The reaction could be reversed by treating the alkane with sulfur. The same thiophene compound was also obtained by treating 4-picoline and 1,2-bis(4-pyridyl)ethane with sulfur (*76*).

1,2-Bis(4-pyridyl)ethane is readily oxidized to the ethylene derivative (*76,549*). The reaction occurs slowly when the ethane is exposed to air. The ethylene compound forms mixed crystals with the ethane, indicating a *trans* configuration for the ethylene. *N*-Bromosuccinimide also reacts with the ethane to give the hydrobromide of the ethylene derivative. The reaction of 1,2-bis(4-pyridyl)ethane with chloranil to give a brown-violet addition product seems to indicate a quinhydrone-type system between the ethane and the ethylene derivatives (*549*).

The only other reported reaction for the synthesis of dipyridylalkenes is the condensation of a pyridine aldehyde with a picoline; in this way 1,2-bis(2-pyridyl)ethylene (*499*) and 1,2-bis(4-pyridyl)ethylene (*76*) have been prepared.

Infrared spectra have been obtained for 1,2-bis(2-pyridyl)ethane (*114*). Ultraviolet spectra for 1,2-bis(4-pyridyl)ethylene and 1,2-bis(4-pyridyl)ethane have been recorded. The ethane, whose spectrum resembles that of 4-picoline, was prepared in pure form by the hydrogenation of the ethylene over palladium (*75*).

Physical properties of these compounds are summarized in Table V-12 (p. 263).

E. ARYLPYRIDINES

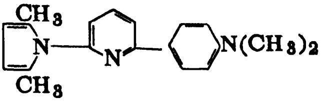
1. Preparation

Many methods used for the preparation of alkylpyridines may be applied to arylpyridines. For example, pyrolysis with zinc dust of 3,5-diphenyl-4-pyridol and 6-methyl-4-phenyl-2-pyridol gives, respectively, 3,5-diphenylpyridine (*551*) and 4-phenyl-2-picoline (*552*). Decarboxylation of *o*-(3-pyridyl)benzoic acid gave 3-phenylpyridine in poor yield (*553*). 2-Phenylpyridine has been obtained by the decarboxylation of 2-(*o*-carboxyphenyl)nicotinic acid (*592*). These methods do not have wide use. The use of organometallic compounds has greater application and is discussed below.

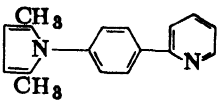
a. Arylations Involving Organometallic Derivatives

2-Phenylpyridine has been prepared by the reaction of phenyllithium with pyridine by Ziegler and Zeiser (*132*); improved directions have been given (*558*). Other aryllithium compounds give the corresponding 2-arylpyridines, such as the *p*-tolyl (*461,554*), *m*-tolyl (*461*), *p*-methoxyphenyl (*555*), 1-naphthyl (*591*), and *p*-(triphenylmethyl)phenyl (*568*) derivatives.

3-Picoline has been phenylated to give 6-phenyl-3-picoline (*64*). However, 4-picoline gave 2-phenyl-4-picolyllithium (*556*). 2-(2,5-Dimethylpyrryl)pyridine was arylated with *p*-dimethylaminophenyllithium to give V-68 (*557*). The closely related V-69 was prepared from pyridine and *p*-(2,5-dimethylpyrryl)phenyllithium (*557*).



(V-68)



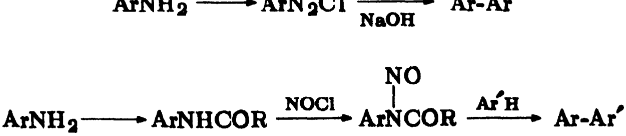
(V-69)

b. Arylations with Diazo Compounds

Pyridine reacts with aryldiazo compounds to give arylpyridines. The reaction involves the replacement of the diazo group by an aromatic nucleus and has received wide application for the preparation of biphenyl derivatives (*559*).

Both the diazonium salt (V-70) and nitrosoacylamine (V-71) have been used in the reaction. When Ar′H in V-70 is pyridine, the

$$\mathrm{ArNH_2} \longrightarrow \mathrm{ArN_2Cl} \xrightarrow[\mathrm{NaOH}]{\mathrm{Ar'H}} \mathrm{Ar\text{-}Ar'} \qquad \text{(V-70)}$$



$$\mathrm{ArNH_2} \longrightarrow \mathrm{ArNHCOR} \xrightarrow{\mathrm{NOCl}} \mathrm{Ar}\overset{\mathrm{NO}}{\overset{|}{\mathrm{N}}}\mathrm{COR} \xrightarrow{\mathrm{Ar'H}} \mathrm{Ar\text{-}Ar'} \qquad \text{(V-71)}$$

alkali may be omitted since the pyridine, if used in excess, furnishes a sufficiently alkaline medium for the reaction. Extensive experimental details are given in the paper by Bachmann and Hoffman (*559*). Other variations of the aryldiazo compound such as phenylazotriphenylmethane (*560*) and 1-aryl-3,3-dimethyltriazenes (*561*) have been employed.

The reaction with pyridine gives a mixture of the 2-, 3-, and 4-arylpyridines in combined yields ranging from 20 to 80% depending upon Ar. The method also influences the yield; for example, a 60% yield of phenylpyridines was obtained when the nitrosoacylamine method was used (*562*), while a 40% yield was obtained with the diazo method (*563*).

The 2-isomer is usually formed in the largest amount; for example, the reaction of pyridine with sodium *p*-nitrobenzenediazotate gives 15% of the 2-isomer and only 5 and 2%, respectively, of the 3- and 4-isomers (*564*). On the other hand, 2-phenylpyridine is obtained in the lowest amount from phenylazotriphenylmethane and pyridine (*560*). It is believed, however, that some of the 2-phenylpyridine may react with the starting azo compound to give a compound, $C_{30}H_{23}N$, of unknown structure. If an appropriate correction is made, the 2-isomer is still formed in the largest amounts (*568*). The isomers can be separated by fractional crystallization of their picrates (*562*). After removal of the 4-isomer as picrate, the 3-isomer may be separated as the acetone-insoluble oxalate (*566*).

Other arylpyridines can be prepared. From *β*-naphthylamine a mixture of *β*-naphthylpyridines was obtained (*561*). Biphenylylpyridines have been prepared by the reactions of aminophenylpyridines with benzene (*565*).

Benzene also reacts with diazo or nitrosoacylamino derivatives of pyridine. Although the preparation of 2-(*o*-hydroxyphenyl)pyridine from sodium 2-pyridinediazotate and phenol has been reported (*645*), 2-aminopyridine usually fails in this reaction. 3-Aminopyridine (*567*) and its derivatives, such as the 2-butoxy, 2-chloro, and 6-chloro (*560*), could be converted to the corresponding phenyl derivatives. 3-Aminoquinoline gives a similar reaction (*560*).

The triazene method was not successful with 3-aminopyridine, and although 3-acetamidopyridine was easily nitrosated, the product was not useful because of its high water solubility. 3-*i*-Butyramidopyridine was used instead, and gave a 39% yield of 3-phenylpyridine (*567*). This is a better method for the preparation of 3-phenylpyridine than the arylation of pyridine.

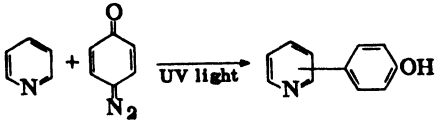
Hey and co-workers have shown that these reactions proceed via a free radical mechanism (*568,569*).

c. *Arylations by Other Free Radical Formers*

The reaction between acyl peroxides and benzene gives diaryl compounds. The yields are usually good, but pyridine gives considerably lower yields due probably to the competitive *N*-oxide formation (*570*). A mixture of the phenylpyridines was obtained from benzoyl peroxide. Nitrobenzoyl peroxide failed to give a product, but pyridine derivatives were isolated from the reactions with *p*-chloro- and *p*-methoxybenzoyl peroxides. 2-Naphthoyl peroxide gave a mixture of the three isomers; while 1-naphthoyl peroxide gave only one isomer (*570*) which was later shown to be 2-(1-naphthyl)pyridine (*591*).

Lead tetrabenzoate and phenyl iodosobenzoate react like benzoyl peroxide. A mixture of the three phenylpyridines is formed (*568*).

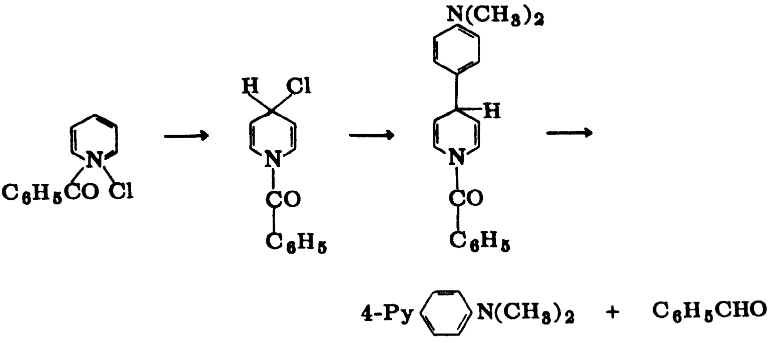
Other free radical reactions which yield arylpyridines are the decomposition of diphenyliodonium chloride in pyridine to give a mixture of the three phenylpyridines (*571*), and the photodecomposition of 4-diazocyclohexadienone in pyridine solution (V-72) (*572*).



(V-72)

d. *Arylation of Quaternary Pyridine Compounds*

Benzoylpyridinium chloride reacts with dimethylaniline to give 4-(*p*-dimethylaminophenyl)pyridine. The reaction was at first run with heat in the presence of a copper-bronze catalyst (*573*), but subsequently it was found to proceed at room temperature in the absence of a catalyst (*574*). A possible mechanism, based on the formation of benzaldehyde during the reaction, has been proposed (V-73) (*573*).

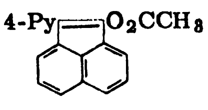


(V-73)

Other dialkylanilines gave the same reaction but with yields lower than the 67% obtained with dimethylaniline (*573*). The reaction can be run with other acylpyridinium salts, a 35% yield of the arylpyridine being obtained from cinnamoylpyridinium chloride and dimethylaniline. Cinnamaldehyde was obtained as the by-product (*575*).

Phenylmagnesium bromide and benzoylpyridinium chloride react to give a 16% yield of 4-phenylpyridine. The probable intermediate, 1-benzoyl-4-phenyl-1,4-dihydropyridine, was isolated in this reaction. A similar reaction of *s*-butylmagnesium bromide with benzoylpyridinium chloride gave 4-(*s*-butyl)pyridine in small yield (*576*). Using a reaction similar to that given by quinoline-1-oxide (*777*), Risaliti obtained in low yield 2-phenylpyridine from the reaction of phenylmagnesium bromide and pyridine 1-oxide (*778*).

A similar type of reaction occurs between acenaphthenone, acetic anhydride, and pyridine to give V-74. Acetaldehyde is formed during the reaction (*577*).



(V-74)

These and related reactions have been reviewed by McEwen and Cobb (*578*). (*Cf.* p. 64.)

2. Properties

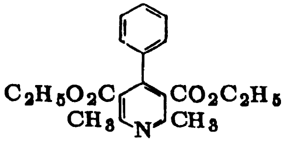
The monophenylpyridines are high boiling liquids, while the di- and polyphenylpyridines are solids. Like the alkylpyridines, the arylpyridines form the expected salts, complexes, and quaternaries at the pyridine nitrogen. The monophenylpyridines are slightly weaker bases than pyridine, 3-phenylpyridine being the least basic (*579*). Polyphenylpyridines are so weakly basic that they form salts with great difficulty (*593*).

Physical properties of the homoarylpyridines are summarized in Table V-13 and of the heteroarylpyridines in Table V-14 (pp. 265 ff.).

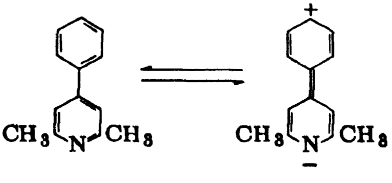
Ultraviolet spectra have been determined for the three monophenylpyridines and their salts (*579*), and for 4-phenyl-2,6-lutidine (*580*). Infrared spectra have been reported for the three monophenylpyridines and 2-(*p*-bromophenyl)pyridine (*568*).

The phenylpyridines resemble the biphenyls in their optical properties, which are determined only by geometrical considerations, the nitrogen in the ring having no influence (*581*). Spectral data indicate that the internuclear bond in both biphenyl and the phenylpyridines is hybrid in nature and possesses double bond character (*582*).

Substituents ortho to the phenyl group in 4-phenylpyridines, as in ethyl 2,6-dimethyl-4-phenyl-3,5-pyridinedicarboxylate (V-75), pre-vent coplanarity of the two rings. When the carbethoxy groups are removed the rings become coplanar, with extensive conjugation (V-76) as shown by ultraviolet spectral data (*580*). This conjugation can serve to explain the formation of highly colored quaternary derivatives of 4-(*p*-dimethylaminophenyl)pyridine (*575*). 4-(4-Quinolyl)-



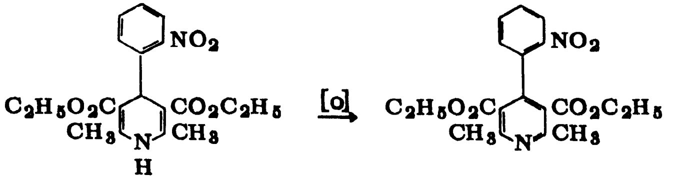
(V-75)



(V-76)

pyridine shows little resonance interaction between the nuclei even in the absence of other groups on the pyridine ring (*580*).

Irradiation of the 4-aryl-1,4-dihydropyridine (V-77) with circularly polarized light produced an optically active compound, which lost its activity on being converted to the pyridine derivative (V-78) (*583*).



(V-77) (V-78)

3. Reactions

a. Oxidation

In acid medium phenylpyridines are oxidized by permanganate to pyridinecarboxylic acids, but in alkaline medium the pyridine ring is attacked and benzoic acid and some traces of pyridinecarboxylic acids are obtained (*584*). In this respect the phenylpyridines resemble the benzylpyridines. These results differ from those obtained with quinoline and isoquinoline, where the benzene ring is always destroyed to yield pyridinedicarboxylic acids.

Isocinchomeronic acid has been obtained by the oxidation of 6-phenyl-3-picoline with permanganate in acid solution (*64*), and isonicotinic acid by a similar oxidation of 4-(*p*-dimethylaminophenyl)pyridine (*573*).

b. Reduction

2-Phenylpyridine has been catalytically reduced to 2-phenylpiperidine (*231,232*). The rate of hydrogenation is about 30% that of pyridine, and further reduction gives 2-cyclohexylpiperidine (*232*). Under the same conditions 4-phenylpyridine was not hydrogenated (*231*).

The introduction of more phenyl groups on the pyridine ring increases the stability of the pyridine ring while decreasing the stability of the benzene ring to reduction. Overhoff and Wibaut (*231*) have shown that the phenyl groups in 2,6-diphenylpyridine, 2,4,6-triphenylpyridine, and 2,3,5,6-tetraphenylpyridine are reduced to give the corresponding cyclohexyl compounds. Pentaphenylpyridine loses a phenyl group on reduction to give a tetracyclohexylpyridine.

c. Aromatic Substitutions

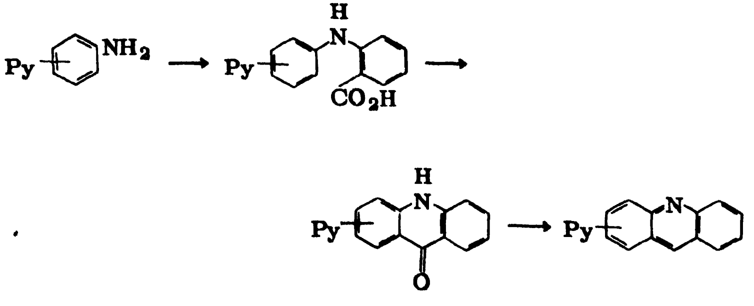
Phenylpyridines are nitrated in the benzene ring to give nitrophenylpyridines. The yield and the position of the nitro group are determined by the point of attachment of the phenyl group on the pyridine ring. 2-Phenylpyridine gives a mixture of 5% ortho, 35% meta, and 42% para 2-(nitrophenyl)pyridines. A 64% yield of 3-(*p*-nitrophenyl)pyridine is obtained from the 3-isomer; while a mixture of 13% ortho, 28% meta, and 38% para is obtained from the 4-isomer (*564*).

The presence of the pyridyl group does not affect the influence of other substituents on the phenyl ring in the introduction of new substituents. 4-(*p*-Dimethylaminophenyl)pyridine is brominated to give 4-(4-amino-3,5 dibromophenyl)pyridine; the two methyl groups are cleaved (*573*). Nitration of the dimethylamino compound gives what may be 4-(2-dimethylamino-3,5-dinitrophenyl)-3-nitropyridine. In this case the pyridine ring is also nitrated (*573*). Methoxyphenylpyridines and acetaminophenylpyridines are readily nitrated in the benzene ring (*585*).

4-(2-Nitrophenyl)-1,4-dihydropyridines undergo photochemical disproportionation to give 4-(2-nitrosophenyl)pyridines (*586*).

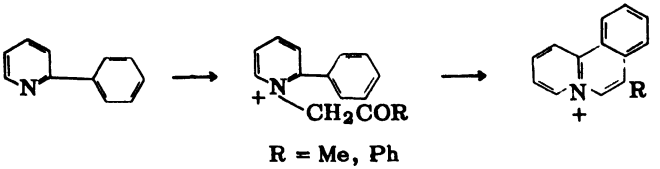
d. Synthesis of Condensed Heterocyclic Systems

Aminophenylpyridines have been converted to quinolylpyridines by the usual methods for the synthesis of quinolines (*585,587,588*). Aminophenylpyridines have been condensed with *o*-chlorobenzoic acid and then cyclized to give pyridylacridines (V-79) (*589*).

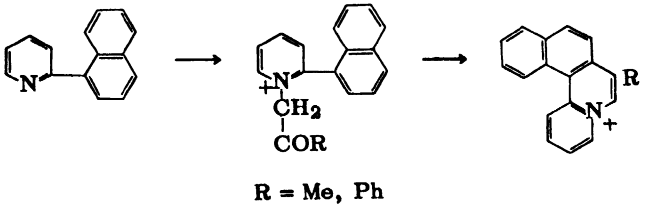


(V-79)

The 2-arylpyridinium salts of halomethyl ketones cyclize on heating in 48% hydrobromic acid to give aromatic systems containing the quinolizinium nucleus. The reaction has been applied to 2-phenylpyridine to give benzo[a]quinolizinium salts (V-80) (*590*) and to 2-naphthylpyridine to give naphtho[1.2-a]quinolizinium salts (V-81). The analogous acridizinium salts are obtained by cyclizing the quaternary derivatives of picolinaldehyde with bromomethylnaphthalenes or phenanthrenes. Analogous reactions are also obtained with arylquinolines and isoquinolines (*591*). (*Cf.* p. 77.)



(V-80)



(V-81)

F. BI- AND POLYPYRIDINES

1. Preparation

Bipyridines, like the alkylpyridines, have been obtained by pyrolytic reactions, but these are of little practical value. 2,3′-Bipyridine has been obtained by pyrolysis of anabasine (*2*) and 2,2′-bipyridine from the zinc dust distillation of 3,5,3′,5′-tetrahydroxy-2,2′-bipyridine (*594*). 2,3′-Bipyridine has been obtained along with other pyridine derivatives from fermented tobacco leaves (*595*).

a. From Alkali Metals or Amides and Pyridine

The reaction of pyridine with sodium amide or sodium in liquid ammonia results in the formation of 2,2′- and 4,4′-bipyridines as well as the expected 2-aminopyridine. The relative amounts of the bipyridines which are formed vary according to conditions; their formation is favored by hydrocarbon solvents when sodium amide is used (*596*). 4,4′-Bipyridine was the only bipyridine by-product isolated from the reaction of sodium with pyridine in liquid ammonia (*272*) and sodium amide with pyridine (*597*).

The reaction of sodium, air, and an excess of pyridine gave a mixture of 2,2′-, 2,3′-, 3,3′-, and 4,4′-bipyridines. These were separated by fractional crystallization of the bases and hydrochlorides (*598*). 2,4′-Bipyridine has also been obtained by this method (*599*). The oxidation can be effected after the initial reaction of sodium with the pyridine compound (*779*).

2,2′-Bipyridine has been obtained in 43% yield from pyridine 1-oxide by treatment with ammonium chloride and sodium in liquid ammonia. A small amount of pyridine was obtained as a by-product (*600*).

b. Ullmann Reaction

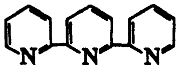
The Ullmann reaction of halo derivatives with copper powder is useful for the preparation of symmetrical bipyridines. Unlike the phenyl derivatives, the bromides give better results than the corresponding chlorides or iodides; even an activated iodo derivative, such as 2-iodo-5-nitropyridine, gives a poor yield of the bipyridine (*601, 602*).

A yield of 60% was obtained from 2-bromopyridine (*601*), but the yields are much lower with substituted 2-bromopyridines (*602–604*). Improved results are given by a sodium chloride-copper mixture in a 1.5:1 ratio (*605*).

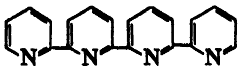
As might be expected, 2,5-dibromopyridine reacts at the 2 position to give 5,5′-dibromo-2,2′-bipyridine (*602*).

Among the other compounds prepared by this method are 4,4′-diethyl-2,2′-bipyridine, 4,4′-diphenyl-2,2′-bipyridine (*603*), 3,3′-, 4,4′-, and 5,5′-dimethyl-2,2′-bipyridines, and 5,5′-dinitro- and 5,5′-dichloro-2,2′-bipyridines (*602*). 6,6′-Dimethyl-2,2′-bipyridine could only be prepared in very low yield from 6-bromo-2-picoline and very active copper (*604*).

2-Bromopyridine and 2,6-dibromopyridine gave a mixture of 2,2′-bipyridine, 2,2′,6′,2″-tripyridine (V-82) and 6,6′-bis(2-pyridyl)-2,2′-bipyridine (V-83) (*606*).

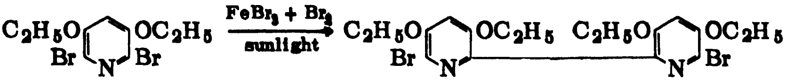


(V-82)



(V-83)

The use of sodium in place of copper did not improve the results with inactive starting materials, such as 2-iodopyridine (*601*) and 6-bromo-2-picoline (*604*). Ferric bromide and bromine have also been used to form bipyridines from 2-bromopyridines in the presence of sunlight (V-84) (*594*).



(V-84)

c. Thermal and Catalytic Dehydrogenation

Pyridine when heated undergoes dehydrogenation to form bipyridines; the 2,2′-isomer was obtained in a quartz tube. By-products included 2,3′-, 3,3′-, and 4,4′-bipyridines, indole, quinoline, an unidentified tripyridine, and other nitrogen derivatives (*607*).

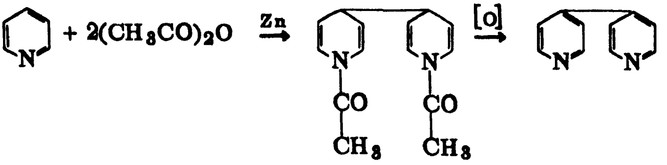
Heating pyridine with ferric chloride at 300–350° gives 2,2′-bipyridine with small amounts of other bipyridines, traces of tripyridines, ammonia, hydrocarbons, and resins (*608,609*). 3-Picoline gave a very low yield of a mixture of 3,3′- and 5,5′-dimethyl-2,2′-bipyridines (*602*).

Iodine has been used in dehydrogenation reactions to form 2,2′-bipyridine from pyridine (*604*) and 6,6′-bis(2-pyridyl)-2,2′-bipyridine from 2,2′-bipyridine (*606*). A nickel-alumina catalyst has been used in the preparation of 2,2′-bipyridine (*610*), 6,6′-dimethyl-2,2′-bipyridine (*604*), 2,2′-biquinoline (*611*), and 1,1′-biisoquinoline (*612*). Purer products are obtained with this catalyst than with iodine (*604*).

Raney nickel has been used for the preparation of 2,2′-bipyridine, 6,6′-dimethyl-2,2′-bipyridine, 4,4′-diethyl-2,2′-bipyridine, and 5,5′(?)-dicarbethoxy-2,2′-bipyridine. 2,4,6-Collidine, 2-aminopyridine, and 3,5-dibromopyridine failed to give bipyridine derivatives under these conditions. Similar bimolecular compounds were obtained from quinoline, 6-methylquinoline, and acridine (*613*).

d. Dimroth Reaction

The use of the Dimroth reaction (*614*) has been mentioned in connection with the synthesis of 4-alkylpyridines (p. 165). When the reaction is stopped after the first stage (V-6), and the 1,1-diacyl-1,1,4,4-tetrahydro-4,4′-bipyridine is oxidized, 4,4′-bipyridine is obtained (V-85) (*614*). The oxidation step gives a 90–95% yield in acetic acid solution (*615*).



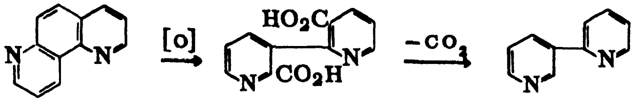
(V-85)

(V-6)

Ethyl chlorocarbonate has been used in place of acetic anhydride (*103*). Changes in procedure have been made without any marked increase in yield (*616*).

e. Decarboxylation Reactions

Phenanthrolines on oxidation yield bipyridinedicarboxylic acids which can be decarboxylated to give bipyridines. For example, 1,7-phenanthroline has been converted to 2,3′-bipyridine (V-86) (*617*).



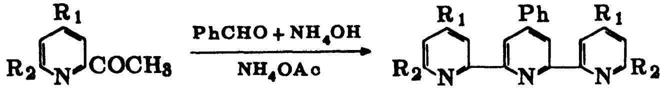
(V-86)

2-Methyl groups on the pyridine rings are more stable to oxidation than the fused benzene ring, so methylbipyridines are obtained from methylphenanthrolines (*618*). $[C^{14}]$-2,2′-Bipyridine has been obtained from $[C^{14}]$-1,10-phenanthroline by this method (*655*). The reactions have been of more use in the elucidation of structures in phenanthroline chemistry than as a preparative method for bipyridines.

Salts of pyridinecarboxylic acids decompose on heating to yield bipyridines; for example, 2,2′-bipyridine was obtained from copper nicotinate (*622*).

f. Condensation Reactions

The Chichibabin synthesis of arylpyridines (Chapter II, pp. 480 f.) has been applied by Frank and Riener to the synthesis of bipyridine derivatives by starting with pyridyl aldehydes and ketones in place of the aryl aldehydes and ketones. A series of polypyridines and arylpolypyridines have been prepared by this method (*619*). The reaction has been applied to the synthesis of a series of 2,2′-6′,2″-tripyridines (V-87) (*603*) and 3,2′,4′,3″-tripyridine. The latter compound was shown to be nicotellin (*620,621*).



(V-87)

R_1 = H, Me, Et, Ph

R_2 = H, Ph

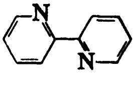
2. Properties and Reactions

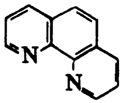
Physical properties of the bi- and polypyridines are summarized in Table V-15 (p. 277).

Although all six of the possible bipyridines have been reported (*598*), later work has thrown serious doubt on the assigned structures. Krumholz (*623*) has shown that the 3,4′-bipyridine of Smith (*598*) is actually 2,4′-bipyridine. This also casts some doubts on bipyridines which had previously been assigned these two structures. A base which may be 3,4′-bipyridine was obtained from the thermal decomposition of pyridine, but the identification was not positive (*623*).

The 3,3′-isomer is a liquid and miscible with water. The others are solids and poorly soluble in water. The thermodynamic properties and basicities of aqueous solutions of 2,2′-bipyridine, analogous 2-heteroarylpyridine compounds (*624*), and 2,2′,6′,2″-tripyridine (*625*) have been reported. The last-named compound is diacidic; the others are monoacidic. In aqueous solution the bipyridines, with the exception of the 2,2′-isomer, show dibasic properties. However, dimethiodides of 2,2′-bipyridine have been prepared. 4,4′- and 2,4′-Bipyridines are the most basic but are weaker bases than pyridine (*579*).

The dipole moments of 2,2′- and 4,4′-bipyridines are very small, indicating a planar nearly *trans* configuration (V-88) for the 2,2′-isomer (*174,626,627*). Since, however, 2,2′-bipyridine and 1,10-phenanthroline (V-89) form metal complexes with the same facility, the *trans* configuration of 2,2′-bipyridine is probably easily transformed to a *cis* (*627*).


(V-88)


(V-89)

Ultraviolet spectral data are available for the six bipyridines, including the questionable 3,4′-bipyridine, and their salts and quaternary derivatives (*579*). There is little similarity to pyridine and the phenylpyridines. The results also indicate less interaction between the rings in the bipyridines than in biphenyl (*627*).

As would be expected, *o*-substituted bipyridines can be resolved, and as with biphenyls and phenylpyridines, their optical stability is based only on geometrical considerations (*581*), although an *o*-nitrogen atom exerts a smaller blocking effect than a —CH— unit (*628*).

Polarographic studies of the bipyridines with the exception of the 3,4′-isomer have been reported (*599*).

2,2′-Bipyridine and structurally related compounds such as 1,10-phenanthroline form complexes with metal ions. 2,2′,6′,2″-Tripyridine and 6,6′-bis(2-pyridyl)-2,2′-bipyridine as well as 2-heteroarylpyridines, where the ring nitrogen is also ortho to the point of attachment, also form these complexes. The literature was reviewed in 1954 (*629*). The colored complexes formed have proved very useful in sensitive analytical tests for the metals.

Substituents on the rings affect the stability of the complexes differently. Although substituents ortho to the nitrogen reduce the stability of ferrous complexes, it is desirable to have two such substituents for a stable and sensitive cuprous reagent (*630*).

Substituents in the 4 position of the pyridine ring increase the sensitivity of the test for ferrous ion. 4,4″-Dimethyl-4′-phenyl-2,2′,6′,2″-tripyridine is a very sensitive agent for ferrous ion (*603*).

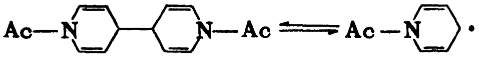
Later work includes stability and other physicochemical studies of 2,2′-bipyridine complexes of cadmium (*631,632*), calcium (*631*), cobalt (*633,634*), copper (*631,633,634*), iron (*634,635*), lead (*631*), magnesium (*631*), manganese (*631,633,636*), nickel (*631,633,634*), ruthenium (*637*), silver (*631*), and zinc (*631–634*). Similar studies are reported on 2,2′,6′,2″-tripyridine complexes of iron (*625,638*), ruthenium, and osmium (*638*). Some of these complexes have been compared with complexes of 1,10-phenanthroline (*631,636*), 2-(2-pyridyl)benzimidazole, 2-(2-pyridyl)imidazoline (*633*), and 1-(2-pyridyl)isoquinoline (*635*).

The bipyridines undergo the usual reactions of pyridine. Amination of 2,2′-bipyridine with sodium amide gives a very low yield of a diamino compound (*604*).

Permanganate oxidation results in mixed cleavage of the rings to yield a mixture of pyridinemonocarboxylic acids. This has been useful in elucidation of the structure of nicotellin (*620,621*).

Studies on the controlled reduction of bipyridines indicate that rings attached at the 4 position are more readily reduced than those attached at the 2 or 3 position. Vigorous reduction reduces both rings, but 4,4′-, 2,2′-, and 3,3′-bipyridines show a decreasing rate of reduction in that order (*639*).

Reduction of 4;4′-bipyridine gives colored complexes which are probably quinhydrone-like in structure (*640,641*). The color of 1,1′-diacetyltetrahydro-4,4′-bipyridine has been shown to be caused by formation of free radicals (V-90) (*98*).



(V-90)

Catalytic reduction of bipyridines in methanol or ethanol solution has resulted in the formation of 1-alkyl-2,2′-bipiperidines and 1,1′-dialkyl-2,2′-bipiperidines, where the alkyl is either methyl or ethyl (*33*).

2,2′-Bipyridine has been oxidized to its 1,1′-dioxide, which in turn can be nitrated to give the expected 4,4′-dinitro derivative (*642*).

2,2′-Bipyridine reacts with phenyllithium to give 6-phenyl-2,2′-bipyridine (*630*) and 6,6′-diphenyl-2,2′-bipyridine (*643*).

As might be expected from steric considerations, the pyridine ring which is attached at its 2 position in mixed bipyridines is quaternized less readily than those attached at the 3 or 4 positions (*644*).

G. TABLES

The physical properties of the various groups of alkyl- and arylpyridines discussed in this chapter are tabulated on the pages that follow.

TABLE V-4. Alkylpyridines[a]

Compound	M.p., °C.	B.p., °C.	d_4^{20}	n_D^{20}	M.p. of picrate, °C.	M.p. of chloro-platinate, °C.	Ref.
2-Picoline	−66.8	129.4	0.9443	1.5010^{25}	165–66.2	195	158,297,354
3-Picoline	−18.3	144.1	0.9566	1.5068^{25}	146–47.5	200–2	78,354
4-Picoline	3.6	145.4	0.9548	1.5058^{25}	167	231	78,354
2-Ethylpyridine	−63.1	148.7		1.4979	107–8.3	167	54,128
3-Ethylpyridine	−76.9	165.0		1.5021	128.1–28.5	208–9	128,543
4-Ethylpyridine	−90.5	167.7	0.9417	1.5020	169.4–69.8	213	78,128
2,3-Lutidine		160.7	0.9419^{25}	1.5057^{25}	188	216	188,650
2,4-Lutidine		157	0.9271^{25}	1.4984	181	220	650,652
2,5-Lutidine		157	0.9261^{25}	1.4982^{25}	169	214	650,653
2,6-Lutidine	−6.1	144.0	0.9226	1.4977^{25}	161	210	354,652
3,4-Lutidine		178.8	0.9385^{25}	1.5099^{25}	163	276	650,667
3,5-Lutidine		171.6	0.9385^{25}	1.5032^{25}	238	255–56	650,667
2-Propylpyridine		164–67.5		1.4930	74.6–75.1	172	120,128,147
3-Propylpyridine		182–84			99.8–100.2		784
4-Propylpyridine		189	0.9250	1.4970	131.0–31.5	204	96,139
2-*i*-Propylpyridine		159.8		1.4915	118.1–18.7	170	78,128
3-*i*-Propylpyridine	−45.7	179.3		1.4965	138.1–38.6	186	128,255
4-*i*-Propylpyridine	−54.9	181.5	0.9382^{25}	1.4962	138.4–39.6	205	78,128,668
3-Ethyl-2-picoline		67–69/15 mm.			140–41		52
4-Ethyl-2-picoline		179–80	0.9130^{25}		141–42	203	78,444
5-Ethyl-2-picoline	−70.3	178.3	0.9215_{20}	1.4970			666,670
6-Ethyl-2-picoline		73–76/12 mm.		1.4920^{25}	127–30		16,785
2-Ethyl-3-picoline		172–73		1.5012^{25}	138–40		785

4-Ethyl-3-picoline		192–93	0.9485	1.5080	144–45		106
5-Ethyl-3-picoline		190			195		647
6-Ethyl-3-picoline		171			144		13
2-Ethyl-4-picoline		172	0.9239_0		120–21		82,669
3-Ethyl-4-picoline		198	0.9556_0				51
2,3,4-Collidine		187	0.9563^{15}	$1.5161^{18.6}$	164	177–79	232,648
2,3,5-Collidine		184	0.9310^{25}	1.5057^{25}	181	146–47	232,650
2,3,6-Collidine		173	0.9220^{25}	1.5018^{25}	144.5–45.5	136–37	232,650
2,4,5-Collidine		188	0.9330^{25}	1.5054^{25}	159–60	189–90	232,650
2,4,6-Collidine	−44.5	170.3	0.9100^{25}	1.4959^{25}	155–56	223–24	165
3,4,5-Collidine		205–207			174	197–98	333
2-Butylpyridine		188–92	0.9135^{15}_{0}		96.7–97.6	146–47	147,656
3-Butylpyridine		39–9/0.5 mm.	0.924_{20}	1.4909	90–90.5	187–88	57,657
4-Butylpyridine		207–209	0.9157	1.4946	112.8–13.8		96
2-*i*-Butylpyridine		177–79		1.4832^{25}	95.5–96	191–93	39
3-*i*-Butylpyridine		68–68.5/8 mm.		1.4912	113–14		783
4-*i*-Butylpyridine		197–99	0.9109	1.4920	121.0–21.5	216	96,120
2-*s*-Butylpyridine		63–68/12 mm.			92–93	176	147,658
4-*s*-Butylpyridine		187			142		120
2-*t*-Butylpyridine	−32.8	169.0		1.4891	104.6–105.2		128
3-*t*-Butylpyridine	−42.9	194.3		1.4965	153.9–54.4		128
4-*t*-Butylpyridine	−39.7	196.3		1.4958	130.9–31.4	212–13	128,290
3-Propyl-2-picoline		200–1			130–31		36
6-Propyl-2-picoline					134.0–34.5		69
4-Propyl-3-picoline		93–94/13 mm.	0.9329	1.5040	136–38		106
4-*i*-Propyl-2-picoline		98–99/40 mm.		1.4939^{25}	119–21		785

(*continued*)

TABLE V-4. Alkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	d_4^{20}	n_D^t	M.p. of picrate, °C.	M.p. of chloroplatinate, °C.	Ref.
5-*i*-Propyl-2-picoline		190–91	0.9114^{15}		167–68	137–38	649
2,4-Diethylpyridine		187–88	0.9338_0		98–100	170–71	78
2,5-Diethylpyridine		81–82/17 mm.			113.5–14.5	146	56
2,6-Diethylpyridine		71–73/17 mm.		1.4890^{25}	115	211–12	659,785
3,4-Diethylpyridine		77–80/9 mm.			139–40		46
3,5-Diethylpyridine		90/5 mm.			170–74	196–200, 245	22
3-Ethyl-2,4-lutidine					137–39	223–25	22
6-Ethyl-2,5-lutidine		181–82			127		671
3-Ethyl-2,6-lutidine		75/13 mm.	0.9120_{20}^{18}		122	178	52,543
4-Ethyl-2,6-lutidine		187.5–88.0	0.9089	1.4964^{25}	121	210–11	650
2-Ethyl-3,5-lutidine		198–99			152	189	672
4-Ethyl-3,5-lutidine		219–20	0.9516	$1.5064^{26.7}$	156–57	276	672
2-*i*-Propyl-3-picoline		181–81.5	0.916	1.4980	149–51		470
6-*i*-Propyl-3-picoline					111–12.5		470
2-*i*-Propyl-4-picoline		184.5–85.0	0.905	1.4908	118.5–19.5		470
2,3,4,5-Tetramethylpyridine		232–34		1.5215^{16}	170–72	209–10	350,673
2,3,4,6-Tetramethylpyridine		203.9	0.9229^{25}	1.5084^{25}	107		650
2,3,5,6-Tetramethylpyridine	81–82	197–98			173–74	178	674
2-Pentylpyridine		206.5–207			73	160	120

3-Pentylpyridine	224–26		1.4892^{25}	78.8–79.2		58,784
4-Pentylpyridine	114/20 mm.		1.4908	104		113
2-*i*-Pentylpyridine	200			105	16	120
3-*i*-Pentylpyridine	107–108/20 mm.			105–105.8		784
4-*i*-Pentylpyridine	222.2–22.8	0.9309	1.4900	115.4–16	214	96,120
3-(2-Methylbutyl)pyridine	86.5–87/8 mm.		1.4929		86–87	783
2-(1-Ethylpropyl)-pyridine	195					694
3-Butyl-2-picoline	222–23			124–25		36
5-Butyl-2-picoline	94–95/11 mm.			135–36		20
6-Butyl-2-picoline					192–94	654
6-*t*-Butyl-2-picoline	179–80	0.9158_0				665
2-Butyl-3-picoline	67/3.5 mm.	0.9134	1.4966	76–77	183–85	32,40
4-Butyl-3-picoline	106–108/14 mm.	0.9264	1.4989	134–55		106
6-Butyl-3-picoline	92.5–93/12 mm.	0.9044	1.4912	91.5		32
2-Butyl-4-picoline	200–202	0.885^{27}_{27}	1.4778	88.5–90.5		133
5-Ethyl-2-propylpyridine				99–100		660
3-Ethyl-4-*i*-propyl-pyridine				134.0–35.5		23
6-*i*-Propyl-2,3-lutidine	197.4–97.8	0.9036	1.4932^{25}	99–100		453
4-Propyl-2,6-lutidine	193–96				185	651
2-Propyl-3,5-lutidine	100–10/8 mm.			150–51		11

(continued)

TABLE V-4. Alkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	d_4^{20}	n_D^t	M.p. of picrate, °C.	M.p. of chloroplatinate, °C.	Ref.
4,5-Diethyl-2-picoline		88–92/20 mm.			162–64		458
4,6-Diethyl-2-picoline		200–10			82	209	153
Pentamethylpyridine		99–100/10 mm.			135–36		43
3-Hexylpyridine		113/10 mm.	0.8978_{25}^{15}	1.4869^{25}	71.5–72		783
4-Hexylpyridine		68.5/0.1 mm.		1.4886	93.5°		113
2-(3-Methylpentyl)-pyridine		134–36/50 mm.				175–76	178
4-(1-Methylpentyl)-pyridine	(mentioned; no data given)						113
3-(4-Methylpentyl)-pyridine		164.5/100 mm.		1.4877	87–87.5		783
5-Pentyl-3-picoline		120/10 mm.			145°		25
4-*i*-Butyl-2,6-lutidine		210–13	0.8961		114–15	208–209	661
6-*s*-Butyl-3,4-lutidine		214	0.8991	1.4947	127–28		194
2,6-Dipropylpyridine		54–56/4 mm.					118
2,6-Di-*i*-propylpyridine	2.5	194.1–94.5/146 mm.			Chloroaurate; 167–67.2		786

3,5-Di-*i*-propylpyridine	46	223–24			134	185	255
3-Heptylpyridine		89/0.5 mm.	0.8930^{15}_{25}	1.4853^{25}	78–78.5		783
4-Heptylpyridine		80/0.1 mm.		1.4818	89		113
5-Hexyl-2-picoline		123/13 mm.		1.4876^{19}	120–21		20
3-(1-Propylbutyl)-pyridine		170/100 mm.		1.4909	113–13.5		783
4-(1-*i*-Propyl-2-methylpropyl)-pyridine		208–10			115		128
5-Butyl-2-propyl-pyridine					70–71		790
6-Butyl-2-propyl-pyridine		228–30					663
6-*t*-Butyl-2-*i*-propylpyridine	–66	94/23 mm.		1.4753			786
3,5-Diethyl-2-propylpyridine		112.5/11.5 mm.		1.4920^{25}	122	166–67	646
3,5-Diisopropyl-2-picoline		220–22	0.9002^{15}		98–100	205	255
3-Octylpyridine		103.5/0.5 mm.	0.8889^{15}_{25}	1.4841^{25}	85.5–86		783
4-Octylpyridine		91/0.1 mm.		1.4858	88.5°		113
2-(2-Methylheptyl)-pyridine	(mentioned; no date given)						700
2-(1-Ethylhexyl)-pyridine	(mentioned; no date given)						175

(*continued*)

TABLE V-4. Alkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	d_4^{20}	n_D^t	M.p. of picrate, °C.	M.p. of chloroplatinate, °C.	Ref.
6-Heptyl-2-picoline		124–25.5/9 mm.		1.4830^{25}	60–62		41
4-Hexyl-2,6-lutidine		249–51/719 mm.				163	651
2,6-Dibutylpyridine		243–44				192.5–93.0	107
2,6-Di-*t*-butylpyridine		100–101/23 mm.		1.5733			146
3-Nonylpyridine		96.7/0.2 mm.	0.8860_{25}^{15}	1.4832^{25}	87.5–88		783
4-Nonylpyridine		103/0.1 mm.		1.4850	104.5		113
2-(2-Methyloctyl)-pyridine	(mentioned; no data given)						58
4-(2-Methyloctyl)-pyridine	(mentioned; no data given)						58
4-Heptyl-2,6-lutidine	(mentioned; no data given)						662
4-(1-Butylpentyl)-pyridine		265–67			114–16		120
4-(1-*i*-Butyl-3-methylbutyl)-pyridine		261			89	180	120
2,6-Di-*t*-butyl-4-picoline	(mentioned; no data given)						786
3-Decylpyridine		135/0.5 mm.	0.8830_{25}^{15}	1.4821^{25}	90.5–91.5		783
4-Decylpyridine		115/0.1 mm.		1.4842	112		113
3,5-Di-*i*-propyl-2-*i*-butylpyridine		258–59	0.8833_{20}^{18}		133	184	255

3,5-Di-*i*-propyl-4-*i*-butylpyridine		255–56	0.8888^{15}		134	210	255
2-Hendecylpyridine		130–32/1 mm.		1.4823^{22}			145
3-Hendecylpyridine		148/0.5 mm.	0.8807_{25}^{15}	1.4814^{25}	93–3.8		783
4-Hendecylpyridine		142–45/1 mm.		1.4794			145
2-(1-Pentylhexyl)-pyridine	(mentioned; no data given)						175
6-(2,6-Dimethyl-heptyl)-2,4-lutidine	65–68	85–88/0.003 mm.					358
2-Dodecylpyridine	5	186/6 mm.	0.8827^{15}	1.4858^{16}	64–65		356
4-Dodecylpyridine	1	186/9 mm.	0.8867^{14}	1.4856^{14}	108–109		356
2-Tridecylpyridine	19	199/10 mm.			78		129
4-Tridecylpyridine	(mentioned; no data given)						58
4-(1-Hexylheptyl)-pyridine	(mentioned; no data given)						58
2-Pentadecylpyridine	29	215/10 mm.			85		129
4-Tridecyl-2,6-lutidine		215–17/13 mm.					664
2-Heptadecylpyridine	37	237/10 mm.			85–86		129
4-Heptadecylpyridine	33						121
4-Pentadecyl-2,6-lutidine		240–42/10 mm.			71	107–8	699

(*continued*)

TABLE V-4. Alkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C	d_4^{20}	n_D^t	M.p. of picrate, °C.	M.p. of chloroplatinate, °C.	Ref.
4-Octadecylpyridine	36	214–16/6 mm.			107		356
2-Nonadecylpyridine	46	247–48/10 mm.			93–94		129
4-Nonadecylpyridine	38	235/1.5 mm.			109–10		356
4-PyCH$(C_{11}H_{23})_2$	35–36	260–65/9 mm.			73–74		356
4-PyCH$(C_{16}H_{33})_2$	68						121
4-PyCH$(C_{17}H_{35})_2$	61–62	280–300/6 mm.			72–73		356
4-PyCH$(C_{18}H_{37})_2$	65	335/5 mm.			75–76		356

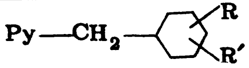
[a] Boiling point is given for 760 mm. unless otherwise indicated. Density is $^{20}_{4}$ unless otherwise indicated. The temperature for n is 20 unless otherwise indicated.

TABLE V-5. Cycloalkylpyridines

Compound	B.p., °C.	d_4^{20}	n_D^{20}	M.p. picrate, °C.	Ref.
2-Cyclopropylpyridine	174–75	0.956^{29}	1.5110^{25}	115–17	37
2-Cyclopentylpyridine	217–18	0.994	1.5263	106.15	470,504
3-Cyclopentylpyridine	245–46	1.005	1.5324	128.0–28.7	42
4-Cyclopentylpyridine	245–46	1.002	1.5306	131–32	42
2-Cyclohexylpyridine	245–46	0.990	1.5246	128–29	470
3-Cyclohexylpyridine	262–63	0.998	1.5297	130–31	42
4-Cyclohexylpyridine	265–66	0.995	1.5284	154–55	470
2-(1-Methylcyclopentyl)pyridine	227–28	0.983	1.5227	108.4–109.8	42
2-Cyclopentylmethylpyridine	240.5–1.5	0.973	1.5178	123.8–24.4	42
3-Cyclopentylmethylpyridine	256–57	0.981	1.5209	120–21.4	42
4-Cyclopentylmethylpyridine	258–59	0.981	1.5209	150.5–51.5	42
2-Cyclohexylmethylpyridine	95–96/2.5 mm.	0.9535		135	31,120,121
3-Cyclohexylmethylpyridine	124–125/6 mm.		1.5224	102.5–103.5	783
4-Cyclohexylmethylpyridine	266			172	121
3-(β-Cyclohexylethyl)pyridine	91/0.1 mm.		1.5170	123.5–24	783
2-Dicyclopentylmethylpyridine	198/32 mm.	0.997	1.5298	109.0–109.5	42
4-Dicyclopentylmethylpyridine	205–15/27 mm.				42
4-Cyclopentyl-2-picoline	251–52	0.984	1.5254	106–107	470
6-Cyclopentyl-2-picoline	228–29	0.977	1.5227	107–109	470
2-Cyclopentyl-3-picoline	235.5–36.5	0.990	1.5297	123–24	470
5-Cyclopentyl-3-picoline				173	647
6-Cyclopentyl-3-picoline	243–44	0.979	1.5242	114–15	470
2-Cyclopentyl-4-picoline	242–43	0.980	1.5238	145–46	470
4-(3-Methylcyclohexyl)-2,6-lutidine	149/7 mm.		1.5120		675
6-(*trans*-2,2,6-Trimethylcyclohexyl)-2,4-lutidine	70–72/0.05 mm. m.p. 24.5	0.9308^{28}	1.5066^{28}	165.0–165.5	193,358
6-(*cis*-2,2,6-Trimethylcyclohexyl)-2,4-lutidine	65–70/0.005 mm.	0.9354	1.5085	174–76	358

(*continued*)

TABLE V-5. Cycloalkylpyridines (*continued*)



Compound Py	Compound R	Compound R'	B.p., °C.	d_4^{20}	$n_D^{t^\circ}$	M.p. picrate, °C.	Ref.
2-Py	2-Me	H	145/14 mm.		1.5163		675
2-Py	4-Me	H	132/8 mm.		1.5110		675
2-Py	3-Me	4-Me	111/3 mm.		1.5132		675
2-Py	2-Me	5-Me	132/6 mm.		1.5137		675
2-Py	3-Me	5-Me	153/18 mm.		1.5112		675
2-Py	3-Et	H	156/17 mm.		1.5100		675
2-Py	4-Et	H	162/17 mm.		1.5093		675
4-Py	4-Et	H	165/17 mm.		1.5112		675
4-Py	2-Me	H	152/15 mm.		1.5163		675
4-Py	3-Me	H	111/3 mm.		1.5140		675
4-Py	4-Me	H	117/3 mm.		1.5130		675
4-Py	2-Me	4-Me	116/3 mm.		1.5112		675
4-Py	3-Me	4-Me	127/3 mm.		1.5136		675
4-Py	2-Me	5-Me	120/3 mm.		1.5117		675
4-Py	3-Me	5-Me	159/18 mm.		1.5094		675
4-Py	3-Et	H	164/17 mm.		1.5121		675
4-Py	3-Me	5-Et	163/13 mm.		1.5104		675
6-Methyl-2-pyridyl	2-Me	H	150/17 mm.		1.5138		675
6-Methyl-2-pyridyl	3-Me	H	111/3 mm.		1.5104		675
6-Methyl-2-pyridyl	4-Me	H	124/9 mm.		1.5097		675
6-Methyl-2-pyridyl	2-Me	4-Me	113/3 mm.		1.5109		675

TABLE V-6. Cycloalkenopyridines

Compound	B.p., °C.	d_4^{20}	n_D^{20}	M.p. picrate, °C.	Ref.
2,3-Cyclopentenopyridine	199.8	1.0359	1.5444	181–82	157,325
3,4-Cyclopentenopyridine	211.8	1.042	1.5439	144	787
2,3-Cyclopenteno-6-picoline	211.9	0.9910_{20}^{23}	$1.5297^{32.6}$	155	787
3,4-Cyclopenteno-5-ethylpyridine	120/11 mm.	1.0080	1.5337	190–92	676
2,3-Cyclohexenopyridine (Bz-tetrahydroquinoline)	92–95/12 mm.	1.030	1.5426	158	325
3,4-Cyclohexenopyridine (Bz-tetrahydroisoquinoline)				144	677
2,3-Cycloheptenopyridine	97–99/11 mm.	1.010	1.5404	130–31.5	323
2,3-Cyclodecenopyridine	165–75/3.7 mm.		1.5370^{26}	154–55	788
2,6-Cyclodecenopyridine	152–58/3.7 mm.		1.5241	165–66	788
2,3-Cyclopentadecenopyridine	125–27/0.005 mm.	0.9726	1.5282	137–38	324

TABLE V-7. Aralkylpyridines

Compound	M.p., °C.	B.p., °C.	$n_D^{20°}$	M.p. picrate, °C.	Ref.
2-Benzylpyridine		276.5–77/730 mm.	1.5790	141–42	83,90,138
3-Benzylpyridine	34	287–88		119	66,244
4-Benzylpyridine		289.0–89.5/730 mm.	1.5810	140.5–41	83,90,138
2-Benzyl-3-picoline		101–106/0.5 mm.			31
6-Benzyl-2-picoline		150/14 mm.		147	88
4-Benzyl-2-picoline		154/13 mm.		117	88
4-Benzyl-2,6-lutidine		167–69/17 mm.	1.5686^{25}	142–43	429
2-Benzyl-4-propylpyridine		203/35 mm.			89
2-(*o*-Methylbenzyl)pyridine		150–60/16 mm.		156–58	87
2-(*p*-Methylbenzyl)pyridine		117–22/2 mm.			31
4-(*o*-Methylbenzyl)pyridine		150–60/16 mm.		136–38	87
2-(2,4-Dimethylbenzyl)pyridine		170–75/16 mm.			87
2-(*p*-*i*-Propylbenzyl)pyridine		135–37/2.5 mm.			31
6-(*o*-Methylbenzyl)-2-picoline		150–60/16 mm.		148–49	87
4-(*o*-Methylbenzyl)-2-picoline		150–60/16 mm.		145°	87
2-(*o*-Chlorobenzyl)pyridine		128–33/3 mm.			31
2-(*p*-Chlorobenzyl)pyridine		108–11/0.5 mm.			31
2-(3,4-Dichlorobenzyl)pyridine		142–48/2 mm.			31
2-(*o*-Hydroxybenzyl)pyridine	98–99	133–39/0.5 mm.			31
2-(*p*-Hydroxybenzyl)pyridine	129.5–30.5	172–78/0.5 mm.			31
4-(*p*-Hydroxybenzyl)pyridine	180–81				259
2-(*o*-Methoxybenzyl)pyridine		134–38/1.5 mm.			31
2-(*p*-Methoxybenzyl)pyridine		145–47/2 mm.			31
2-(*p*-Acetylbenzyl)pyridine		160–65/1 mm.	1.5975^{27}	137–38	201
4-(*p*-Acetylbenzyl)pyridine		165–70/1 mm.	1.5864^{28}		201
2-(*o*-Nitrobenzyl)pyridine		160–70/0.4 mm.			433
2-(*p*-Nitrobenzyl)pyridine	81			184–85	259,433
3-(*p*-Nitrobenzyl)pyridine	88			145–46	692
4-(*o*-Nitrobenzyl)pyridine		160–70/0.4–0.6 mm.		156–57	433

4-(*p*-Nitrobenzyl)pyridine	72–73			167–68	259,433
2-(2,4-Dinitrobenzyl)pyridine	91–93			164–65	259,433
4-(2,4-Dinitrobenzyl)pyridine	80–81			152–53	433
2-(*o*-Aminobenzyl)pyridine	69–70				661
2-(*p*-Aminobenzyl)pyridine	60			141 (mono) 182–84 (di)	199,259
4-(*p*-Aminobenzyl)pyridine	158–59			153 (mono) 194 (di)	199,259
2-(2-Nitro-4-aminobenzyl)pyridine	106–12				433
4-(2-Nitro-4-aminobenzyl)pyridine	130–31				433
2-(2,4-Diaminobenzyl)pyridine	161				661
2-(*p*-Dimethylaminobenzyl)pyridine		135–40/1 mm.			31
$p\text{-}(\mathrm{Me_2NCH_2CH_2})\mathrm{C_6H_4CH_2Py}\text{-}2$		145–51/1 mm.	1.5618^{25}		59
$p\text{-}(\mathrm{Me_2N}\overset{\mathrm{Me}}{\mathrm{CH}})\mathrm{C_6H_4CH_2Py}\text{-}2$		157–61/3 mm.	1.5592^{27}		59
$p\text{-}(\mathrm{Me}\overset{\mathrm{NH_2}}{\mathrm{CH}})\mathrm{C_6H_4CH_2Py}\text{-}2$		154–60/2 mm.	1.5762^{28}		59
$o\text{-}(\mathrm{Me_2NCH_2CH_2O})\mathrm{C_6H_4CH_2Py}\text{-}2$		161/1.5 mm.	1.5440^{28}		555
$p\text{-}(\mathrm{Me_2NCH_2CH_2O})\mathrm{C_6H_4CH_2Py}\text{-}2$		149/1 mm.	1.5536^{25}		555
4-(*p*-Nitrobenzyl)-2,6-lutidine	135.5–6.5				429
4-(2,4-Dinitrobenzyl)-2,6-lutidine	139.5				429
4-(*p*-Aminobenzyl)-2,6-lutidine	132–33				429
4-(*p*-Hydroxybenzyl)-2,6-lutidine	163–64				429
2-(1-Naphthylmethyl)pyridine		181/0.9 mm.		166–67	140
4-(1-Naphthylmethyl)pyridine	78			175	88
6-[2-(2,6,6-Trimethyl-tetrahydropyranyl)methyl]-2,4-lutidine		94–95/0.1 mm.	1.4992^{25}		358
1-(2-Pyridylmethyl)-6,7-methylenedioxyisoquinoline	133–35	133–35			686

(*continued*)

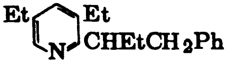
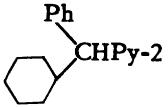
TABLE V-7. Aralkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	$n_D^{t^\circ}$	M.p. picrate, °C.	Ref.
1-(2-Pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline	117–19				686
1-(4-Pyridylmethyl)-6,7-methylenedioxyisoquinoline	171–73				531
1-(4-Pyridylmethyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline	134–40				531
2,4-Dibenzylpyridine		220–22/12 mm.			86
2,6-Dibenzylpyridine	73–75			177	86
3,5-Dibenzylpyridine	89				687
3,5-Di(o-methylbenzyl)pyridine	40.5			182–83	688
3,5-Di(*m*-methylbenzyl)pyridine	65–66.5			116–17	688
3,5-Di(*p*-Methylbenzyl)pyridine	108.5			156–58	688
3,5-Di(*p*-*i*-propylbenzyl)pyridine	76–77			111–13	689
2,3,5 or 3,4,5-Tribenzylpyridine	278–80				687
2,3,5 or 3,4,5-Tris(*p*-*i*-propylbenzyl)pyridine	299–302				689
2-Phenethylpyridine	−0.5	145/10 mm.		125.5–27	120,127
3-Phenethylpyridine		126–30/2.75 mm.		144.2	64
				150–52	691
4-Phenethylpyridine	70–71			165	120,127
2-Phenethyl-4-picoline		290–95		154–56	680,681
6-Phenethyl-2-picoline		165/23 mm.		125	120
5-Ethyl-2-phenethylpyridine		309–12			120
2-(*m*-Methylphenethyl)pyridine		220/35 mm.		131	678
2-(*p*-Methylphenethyl)pyridine		294–96		Chloroplatinate: 180	679
4-(*m*-Methylphenethyl)pyridine		220/60 mm.		122	678
4-(*p*-Methylphenethyl)pyridine		200/80 mm.			680
4-(*p*-*i*-Propylphenethyl)pyridine		185–95/33 mm.			678

4-(*o*-Chlorophenethyl)pyridine		177–82/9–10 mm.			127
2-(*o*-Hydroxyphenethyl)pyridine	193–94				449
2-(*p*-Hydroxyphenethyl)pyridine	154–55				449
2-(*p*-Methoxyphenethyl)pyridine		183–84/11 mm.			127
4-(*o*-Hydroxyphenethyl)pyridine	163–64				449
4-(*p*-Hydroxyphenethyl)pyridine	169–70				449
4-(*p*-Methoxyphenethyl)pyridine	54–55				127
2-(HO)-3,5-$(I)_2C_6H_2CH_2CH_2$Py-2	126–28				449
2-(HO)-3,5-$(Br)_2C_6H_2CH_2CH_2$Py-2	116–17				449
3,5-$(I)_2$-4-$HOC_6H_2CH_2CH_2$Py-2	170–71				449
2-(HO)-3,5-$(I)_2C_6H_2CH_2CH_2$Py-4	145–46				449
3,5-$(I)_2$-4-$HOC_6H_2CH_2CH_2$Py-4	161–62				449
2-(*o*-Nitrophenethyl)pyridine	184				317
2-(*m*-Nitrophenethyl)pyridine	76				317
2-(*p*-Nitrophenethyl)pyridine	96			171	317
4-(*p*-Nitrophenethyl)pyridine	85				498
2-(*o*-Aminophenethyl)pyridine	61				317
2-(*p*-Aminophenethyl)pyridine	57				317
4-(*p*-Aminophenethyl)pyridine	111–12				127
2-(3-Nitro-4-aminophenethyl)pyridine	150				317
o-$(CH_3)_2NCH_2CH_2OC_6H_4CH_2CH_2$Py-4		160–64/1 mm.			555
2-[β-(1-Naphthyl)ethyl]pyridine	176–77				127
4-[β-(1-Naphthyl)ethyl]pyridine	47–51	223–25/7 mm.			127
2-[β-(2-Thienyl)ethyl]pyridine		115–19/1 mm.	1.5428^{25}	130.5–32	63
2-[β-(2-Furyl)ethyl]pyridine		100–101/1 mm.	1.5132^{25}	112–13.5	63
2-[β-(1-Pyrryl)ethyl]pyridine		148–50/10 mm.		129.5–30.4	307
2,6-Diphenethylpyridine		150–70/0.01 mm.		155	117
Ph(Me)CHPy-2		142–43/12 mm.			334
$Ph(CH_2)_3$Py-2		140/2.5 mm.	1.5571^{25}	108.5	121,553
$Ph(CH_2)_3$Py-4		150–52/5–6 mm.			127

(*continued*)

TABLE V-7. Aralkylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	$n_D^{t^\circ}$	M.p. picrate, °C.	Ref.
Ph(Me)CHCH$_2$Py-2		199/2 mm.		125	120,121
Ph(Et)CHPy-2		104–6/0.01 mm.			334
Ph(CH$_2$)$_4$Py-2		142–45/2 mm.	1.5472^{25}		553
Ph(CH$_2$)$_4$Py-4	47–49	170–71/5–6 mm.			127
		185/26 mm.			130
Ph(Pr)CHPy-2		158–62/12 mm.			334
Ph(*i*-Pr)CHPy-2		153–55/12 mm.			334
p-ClC$_6$H$_4$(*i*-Pr)CHPy-2		179–80/14 mm.			334
Ph(CH$_2$)$_5$Py-2	33–35	169–72/7.8 mm.			127
Ph(*i*-Bu)CHPy-2		157–62/12 mm.			334
Ph(*i*-Am)CHPy-2		172–74/12 mm.			334
					334
	73–74	148–51/0.01 mm.			334

$$\mathrm{PyCH}\langle^{R}_{R^1}$$

Py	R	R^1	M.p., °C.	B.p., °C.	$n_D^{t^\circ}$	M.p. picrate, °C.	Ref.
2-Py	Ph	Ph	60–61	157–59/0.02 mm.		172	243,334
	PhCH$_2$	PhCH$_2$		198/5 mm.		130	120
	Ph	PhCH$_2$		170–71/0.03 mm.			334
	Ph(CH$_2$)$_2$	Ph(CH$_2$)$_2$		212/2.5 mm.		102	121
	Ph	*p*-ClC$_6$H$_4$	82–83	182–85/0.01 mm.			334

	p-ClC_6H_4	p-ClC_6H_4		194–95/0.01 mm.			334
	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$		182–83/0.01 mm.			334
	Ph	$3,4(Me)_2C_6H_3$	81–82	194–95/0.03 mm.			334
	p-HOC_6H_4	p-HOC_6H_4	254				684
	p-$MeOC_6H_4$	p-$MeOC_6H_4$		198–201/0.02 mm.			334
	p-HOC_6H_4	2-Me-4-HOC_6H_3	206				684
	p-HOC_6H_4	3-Me-4-HOC_6H_3	247				684
	p-HOC_6H_4	2-i-Pr-4-HO-5-MeC_6H_2	251				684
	Ph	2-Thienyl				Hydrochloride: 165	47
3-Py	Ph	Ph	78–79				682,683
	$PhCH_2$	$PhCH_2$		198–201/3 mm.			64
	p-HOC_6H_4	p-HOC_6H_4	238				684
4-Py	Ph	Ph	125				243
	$PhCH_2$	$PhCH_2$	74.6–75.6	176–81/1 mm.		163.4–64	147
	$PhCH_2CH_2$	$PhCH_2CH_2$		196/2 mm.			179
	p-HOC_6H_4	p-HOC_6H_4	261				684
6-Me-2-Py	$PhCH_2$	$PhCH_2$		173/0.2 mm.	1.5832	161–62	117
	p-HOC_6H_4	p-HOC_6H_4	239				684
6-(2,3-Diphenylpropyl)-2-picoline						145–46	117
9-(2-Pyridyl)fluorene				187–200/0.1 mm.		182–84	334
9,9-Di(2-pyridyl)fluorene			213–14				334

(continued)

TABLE V-7. Aralkylpyridines (*continued*)

Compound: $\mathrm{Py{-}C(R)(R^1)(R^2)}$				M.p., °C.	B.p., °C.	$n_D^{t°}$	M.p. picrate, °C.	Ref.
Py	R	R¹	R²					
2-Py	Me	Ph	Ph	50–51	142–44/0.1 mm.			47
	Et	Ph	Ph		140–42/0.1 mm.			47
	Pr	Ph	Ph		128–30/0.02 mm.			47
	Bu	Ph	Ph	(mentioned; no data given)				47
	Ph	Ph	Ph	241				131
3-Py	Ph	Ph	Ph	269–70				144
	Ph	Ph	p-$\mathrm{PhC_6H_4}$	195–96				144
6-Me-2-Py								
	Ph	Ph	Ph	153–54				144
	Ph	Ph	p-$\mathrm{PhC_6H_4}$	188–89				144

TABLE V-8. Alkenylpyridines

Compound	B.p., °C.	d_4^{20}	n_D^{20}	M.p. picrate, °C.	M.p. chloroplatinate, °C.	Ref.
2-Vinylpyridine	159–60	0.9985_0	1.5495		174	538
3-Vinylpyridine	67–68/18 mm.		1.5530	143–44	158–60	469,538
4-Vinylpyridine	65/15 mm.		1.5499			538
2-Propenylpyridine	189–90			165–66	185–86	78,698
4-Propenylpyridine	200–2			169–70	206	697
2-*i*-Propenylpyridine	63–67/10 mm.	0.9962_{25}^{25}	1.5221^{25}	148–49	163–64	463,465
3-*i*-Propenylpyridine	10/75 mm.	0.9775_{25}^{25}	1.5381^{25}	156	152	255,465
4-*i*-Propenylpyridine	82/15 mm.					696
2-Allylpyridine	63–64/15 mm.		1.513			440
3-Allylpyridine	69–70/15 mm.			109.2–9.6		136
6-Vinyl-2-picoline	73/21 mm.		1.5320^{25}	160.5		474
3-Vinyl-4-picoline				Hydrochloride: 164–66		480
5-Vinyl-2-picoline	75/15 mm. m.p. –12	0.950_{20}	1.5454	157–58		538
2-(1 or 2-Butenyl)pyridine	197			153	162–63	120
2-(3-Butenyl)pyridine	188–92	0.9715^0	1.511^{16}	177	163–64	120
3-(3-Butenyl)pyridine	99–102/25 mm.			90.6–91		784
3-Methallylpyridine	74.2–74.4/8 mm.			101–2		441
2-*i*-Propenyl-4-picoline	98–101/23 mm.		1.5352	165–67		470
5-Ethyl-2-vinylpyridine	95–97/18 mm.		1.5383	129.5–30.5		472
4,6-Dimethyl-2-vinylpyridine	76–78/13 mm.					292
3-(3-Pentenyl)pyridine	93–94/12 mm.					179
5-(1-Butenyl)-2-picoline	98–99/12 mm.			162	169–70	660
5-Ethyl-2-propenylpyridine	103/12 mm.			129	156–57	698
3,5-Dimethyl-2-propenylpyridine	99–100/10 mm.			179–80		24

(continued)

TABLE V-8. Alkenylpyridines (*continued*)

Compound	B.p., °C.	d_4^{20}	n_D^{20}	M.p. picrate, °C.	M.p. chloroplatinate, °C.	Ref.
4,6-Dimethyl-2-propenylpyridine	110–11/12 mm.				205–206	445
3-Ethyl-4-(3-butenyl)pyridine	125–30/20 mm.					120
3-(1-Heptenyl)pyridine	250–60			102–2.4		136
5-Butyl-2-propenylpyridine				137–38		790
2-(10-Dodecenyl)pyridine	152–53/4 mm.		1.4907^{25}	64.5–65.5		693
2-(11-Dodecenyl)pyridine	158–59/4 mm.	0.8941^{16}	1.4926^{25}	46–46.5		356,693
4-(11-Dodecenyl)pyridine	156/2 mm.	0.9006^{13}	1.4940^{19}	102–3		356
2,4-Divinylpyridine	(mentioned; no data given)					473
2,5-Divinylpyridine	(mentioned; no data given)					473
2,6-Divinylpyridine	88–89/16 mm.		1.5710^{25}	140.5		474
2-(1,3-Butadienyl)pyridine	70/1 mm.			146.5–47.9		690
2-(2,3-Butadienyl)pyridine	85–88/12 mm.					440
2-(1-Vinyl-3-butenyl)pyridine	98–101/15 mm.		1.526^{16}			440
3,5-Di(*i*-propenyl)pyridine	242–43 m.p. 50			156		255
$(CH_3CH{=}CHCH_2)_2CHPy\text{-}2$	132–34/12 mm.					179
$(CH_2{=}CHCH_2CH_2)_2CHPy\text{-}4$	184–88/39 mm.		$1.5270^{28.3}$	112.5–13		42
2-(1,3,5-Heptatrienyl)pyridine	135–40 m.p. 55			162		119

TABLE V-9. Cycloalkenylpyridines

Compound	B.p., °C.	$d_4^{20°}$	$n_D^{20°}$	M.p. picrate, °C.	Ref.
2-(1-Cyclopentenyl)pyridine	141.5/35 mm.	1.038	1.5795	183–84	470
3-(1-Cyclopentenyl)pyridine	139/21 mm.	1.047	1.5800	170.8–71.5	42
4-(1-Cyclopentenyl)pyridine				180–82	470
4-(1-Cyclopentenyl)-2-picoline	157/31 mm.	1.024	1.5704	106–7	470
6-(1-Cyclopentenyl)-2-picoline	144/32 mm.	1.015	1.5702	107–9	470
2-(1-Cyclopentenyl)-3-picoline	148/31 mm.	1.027	1.5722	123–24	470
6-(1-Cyclopentenyl)-3-picoline	156/31 mm. m.p. 59–60			114–15	470
2-(1-Cyclopentenyl)-4-picoline	154/30 mm. m.p. 34–36			145–46	470
2-(1-Cyclohexenyl)pyridine	155/31 mm.	1.033	1.5737	159–60	470
3-(1-Cyclohexenyl)pyridine	161/31 mm.	1.040	1.5717	175.5–76.5	42
4-(1-Cyclohexenyl)pyridine	165/31 mm.	1.044	1.5733	180–81	470
2-(3-Cyclohexenyl)pyridine	66–67/0.4 mm.	1.0150_{20}	1.5444	114.5–15	459,460
3-(3-Cyclohexenyl)pyridine	98–100/3 mm.			117–18.5	459
2-(2-Methyl-3-cyclohexenyl)pyridine	132–33/20 mm.	0.9958_{20}	1.5374	110–11	460
2-(4-Methyl-3-cyclohexenyl)pyridine	141–41.5/20 mm.	0.9956_{20}	1.5382	104–8	460
2-(2,5-Dimethyl-3-cyclohexenyl)pyridine	139–42/20 mm.	0.9784_{20}	1.5284		460
2-(3,4-Dimethyl-3-cyclohexenyl)pyridine	128–30/6 mm.	0.9937_{20}	1.5410	106.5–7.5	459,460
2-(2,5-Endomethylene-3-cyclohexenyl) pyridine	133–34/20 mm.	1.0621_{20}	1.5578	142–43	460

(continued)

TABLE V-9. Cycloalkenylpyridines (*continued*)

Compound	B.p., °C.	$d_4^{20°}$	$n_D^{20°}$	M.p. picrate, °C.	Ref.
2-(2,5-Endoethylene-3-cyclohexenyl-pyridine	150–54/20 mm.	1.0692_{20}	1.5590	123	460
2,4-Dimethyl-6-(2,6,6-trimethylcyclohexenyl)pyridine	88–90/0.004 mm.	0.9615^{18}	1.5263^{18}		358
2,4-Dimethyl-6-(2,6,6-trimethyl-2-cyclohexenyl)pyridine	60–62/0.003 mm.	0.9534^{18}	1.5242^{18}		358
2-[2-Methyl-4-(2,6,6-trimethylcyclohexenyl)3,4-butadienyl]pyridine	135–42/0.003 mm. m.p. 41–46			155	119
4-Methyl-2-[2-methyl-4-(2,6,6-trimethylcyclohexenyl)-3,4-butadienyl]pyridine	140/0.003 mm.			two forms 156 166	119

TABLE V-10. Aralkenylpyridines

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	M.p. methiodide, °C.	Ref.
2-Stilbazole	91	194/14 mm.	207	230-31	701,702
4-Stilbazole	127	208–10/33 mm.	213	220–21	447,703 704
2-(1-Phenylethenyl)pyridine		292–95	155		463,705
3-1(1-Phenylethenyl)pyridine	78–82	204–10/23 mm.			706
4-(1-Phenylethenyl)pyridine		300–5			705
3-Methyl-2-stilbazole	55		198		278
4-Methyl-2-stilbazole		160/1 mm.	192–93		681
6-Methyl-2-stilbazole	123		217–19		707
3′-Methyl-2-stilbazole		220/45 mm.	214–15		678
4′-Methyl-2-stilbazole	87		193–94		279,679
3′-Methyl-4-stilbazole		220–25/35 mm.	194–96		678
4′-Methyl-4-stilbazole	101–2				680
α-Methyl-2-stilbazole		144–45/1 mm.			448
α-Methyl-4-stilbazole	72–73				448
4,6-Dimethyl-2-stilbazole		188–89/9 mm.	240–41		714
4,4′-Dimethyl-2-stilbazole	202				708
6,4′-Dimethyl-2-stilbazole	144–45		226		709
5-Ethyl-2-stilbazole	58.5	116/.03 mm.	203		20,451
4′-*i*-Propyl-2-stilbazole	47		189–90		711
4′-*i*-Propyl-4-stilbazole	65–67		188–90		678
4-Ethyl-6-methyl-2-stilbazole		205/2 mm.	233		712
5-Ethyl-4′-methyl-2-stilbazole	94		201–2		708
5-Butyl-2-stilbazole		167–68/0.16 mm.	167–68		20
6-Methyl-4-propyl-2-stilbazole			255		454
6-*i*-Propyl-5-methyl-2-stilbazole		179–80/2 mm.	162–63		453
4,5-Diethyl-2-stilbazole		146–50/0.1 mm.	241–43		458

(*continued*)

TABLE V-10. Aralkenylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	M.p. methiodide, °C.	Ref.
5-Hexyl-2-stilbazole	46–47	163–68/0.01 mm.			20
5-Butyl-α-ethyl-2-stilbazole		153–65/0.2 mm.	106–107		790
2-(4-Phenyl-1,3-butadienyl)pyridine	123–24		122		285
4-(4-Phenyl-1,3-butadienyl)pyridine	137–38		161–62		285,710
6-(4-Phenyl-1,3-butadienyl)-2-picoline	110–11		229		285
6-(4-Phenyl-1,3-butadienyl)-2,4-lutidine		238–43/21 mm.			710
4-[2-(2-Furyl)ethenyl]pyridine				202–3	703
4-[2-(2-Thienyl)ethenyl]pyridine				232–33	703
2-[2-(4-Quinolyl)ethenyl]pyridine				249–50	713
4-[2-(4-Quinolyl)ethenyl]pyridine				264–65	713
2-(1,2-Diphenylethenyl)pyridine			165–66		284
4-(1,2-Diphenylethenyl)pyridine	86		188–89		284
2-[1-Phenyl-2-(2-thienyl)ethenyl]-pyridine	77	290–92/50 mm.	183		450
2-[2-(5-Acenaphthyl)-1-phenylethenyl]-pyridine	140	322/45 mm.	236		450
2′-Chloro-2-stilbazole	76–77	108–10/2 mm.		230–31	492
3′-Chloro-2-stilbazole				293–94	702
4′-Chloro-2-stilbazole	82.5–83				524
2′-Chloro-4-stilbazole				218–19	703
4′-Chloro-4-stilbazole				250–51	703
2-[2-(o-Chlorophenyl)-1-phenylethenyl]-pyridine	83		175		450
2-[2-(*p*-Chlorophenyl)-1-phenylethenyl]-pyridine	92		177		450
4-[2-(o-Chlorophenyl)-1-phenylethenyl]-pyridine		210–12/3 mm.	147		450
4-[2-(*p*-Chlorophenyl)-phenylethenyl]-pyridine	89	203–4/0.5 mm.	170		450

cis-2′-Hydroxy-2-stilbazole				184–85	492
trans-2′-Hydroxy-2-stilbazole				253–54	492
3′-Hydroxy-2-stilbazole				221–22	702
4′-Hydroxy-2-stilbazole				269–70	702
cis-2′-Hydroxy-4-stilbazole				224–25	492
trans-2′-Hydroxy-4-stilbazole				235–36	492
3′-Hydroxy-4-stilbazole				260–61	703
4′-Hydroxy-4-stilbazole				265–66	703
4′-Hydroxy-6-methyl-2-stilbazole	232				118
4′-Methoxy-2-stilbazole	75–75.5			242–43	493,702
2′-Methoxy-4-stilbazole				194–95	703
4′-Methoxy-4-stilbazole	135			214–15	493,703
2′-Ethoxy-2-stilbazole				252–53	716
2′-Methoxy-3-methyl-2-stilbazole	60		208–9	205	278
4′-Methoxy-3-methyl-2-stilbazole	88		196–97	234	278
4′-Methoxy-6-methyl-2-stilbazole	59–62				452
4′-Butoxy-6-methyl-2-stilbazole	85				715
4′-Methoxy-α-methyl-2-stilbazole		195–200/10 mm.			448
4′-Methoxy-α-methyl-4-stilbazole	83–84				448
4,6-Dimethyl-4′-methoxy-2-stilbazole		230–35/20 mm.			710
p-MeOC$_6$H$_4$CH : C(Ph)Py-2	115		169		450
p-MeOC$_6$H$_4$CH : C(Ph)Py-4	113		198		450
2′-Acetoxy-2-stilbazole		180–81/3.5 mm.		201–2	492
4′-Acetoxy-2-stilbazole	114–15			230–31	492
cis-2′-Acetoxy-4-stilbazole	118–19			228–29	492
trans-2′-Acetoxy-4-stilbazole	197–98				492
4′-Acetoxy-4-stilbazole	167–68				492
o-CH$_3$CO$_2$C$_6$H$_4$CH : C(Ph)Py-2	135			179	450
o-CH$_3$CO$_2$C$_6$H$_4$CH : C(Ph)Py-4	153				450
3′,4′-Dihydroxy-2-stilbazole				270–71	702

(*continued*)

TABLE V-10. Aralkenylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	M.p. methiodide, °C.	Ref.
3′,4′-Methylenedioxy-2-stilbazole	111–12	180–81/2 mm.		274–75	492
				295	702
3′,4′-Methylenedioxy-4-stilbazole				283–84	703
3′-Methoxy-2′-hydroxy-4-stilbazole				247–48	703
3′-Methoxy-4′-hydroxy-2-stilbazole				275–76	702
3′-Methoxy-4′-hydroxy-4-stilbazole				275–76	703
3′-Ethoxy-2′-hydroxy-2-stilbazole				242–43	702
3′-Ethoxy-2′-hydroxy-4-stilbazole				236–37	703
3′-Ethoxy-4′-hydroxy-2-stilbazole				260–61	702
3′-Ethoxy-4′-hydroxy-4-stilbazole				275–76	703
2′,5′-Dimethoxy-2-stilbazole				244–45	702
2′,5′-Dimethoxy-4-stilbazole				246–47	703
3′,4′-Dimethoxy-2-stilbazole				244–45	702
3′,4′-Dimethoxy-4-stilbazole				253–54	703
3′,4′-Diethoxy-2-stilbazole				246–47	702
				231–32	716
3′,5′-Diiodo-4′-hydroxy-6-methyl-2-stilbazole	185–87				449
3′,5′-Diiodo-4′-acetoxy-6-methyl-2-stilbazole	188–89				449
6′-Cyano-6-methyl-2-stilbazole	131				118
cis-2′-Nitro-2-stilbazole	95				491
trans-2′-Nitro-2-stilbazole	101		211–12	229–30	491,492
3′-Nitro-2-stilbazole	131–32			251–53	492
4′-Nitro-2-stilbazole	140–41			253–54	492
2′-Nitro-4-stilbazole	105				498
3′-Nitro-4-stilbazole	144–45			299–300	492
4′-Nitro-4-stilbazole	171		294	235–36	498,703

3-Methyl-2′-nitro-2-stilbazole	155		190–91		278
3-Methyl-3′-nitro-2-stilbazole	124		208–9		278
3-Methyl-4′-nitro-2-stilbazole	145		298–99		278
6-Methyl-2′-nitro-2-stilbazole	55–57		227–28		718
6-Methyl-4′-nitro-2-stilbazole			135		118
α-Methyl-3′-nitro-2-stilbazole	195–96				448
α-Methyl-4′-nitro-2-stilbazole	95–96				448
α-Methyl-3′-nitro-4-stilbazole	114–15				448
α-Methyl-4′-nitro-4-stilbazole	110–11				448
4′-Methyl-3′-nitro-2-stilbazole	137		223		498
5′-Chloro-2′-nitro-2-stilbazone	92				546
2′,4′-Dinitro-2-stilbazole	159				280
3′,4′-Dinitro-2-stilbazole	168				317
2′-Amino-2-stilbazole	98–99	197–200/12 mm.	158–59		491
3′-Amino-2-stilbazole	103–4				719
4′-Amino-2-stilbazole	138–39				490
2′-Amino-4-stilbazole			Hydrochloride: 205		720
3′-Amino-4-stilbazole	189–90				719
4′-Amino-4-stilbazole	138–39				490
	285				489
4′-Amino-4-methyl-2-stilbazole	119				721
2′-Amino-6-methyl-2-stilbazole	136–37				718
4′-Amino-6-methyl-2-stilbazole	139–40				718
4′-Dimethylamino-2-stilbazole				273–74	702
4′-Dimethylamino-4-stilbazole	240–41			258–59	703,719
4′-Dimethylamino-α-methyl-4-stilbazole	164–65				448
4′-Dimethylamino-3-methyl-2-stilbazole	93		202	255	278
4′-Diethylamino-2-stilbazole				246–47	702
4′-Diethylamino-4-stilbazole				221–22	703
3′-Bromo-4′-dimethylamino-2-stilbazole				232–33	702

(continued)

TABLE V-10. Aralkenylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	M.p. methiodide, °C.	Ref.
3′-Dimethylaminoethoxy-2-stilbazole	137–38				555
4′-Dimethylaminoethoxy-2-stilbazole	70–71	182–92/1 mm.			555
2′-Azoxy-bis(3-methyl-2-stilbazole)	174				278
3′-Azoxy-bis(3-methyl-2-stilbazole)	157				278
4′-Azoxy-bis(3-methyl-2-stilbazole)	220				278
3′-(2,5-Dimethylpyrryl)-2-stilbazole	132–33				719
2-[2-(*o*-Aminophenyl)-2-phenylethenyl]-pyridine	139–40		188–89		260
2-[2-(*o*-Aminophenyl)-2-(*p*-methoxyphenyl]-ethenyl]pyridine			168–69		260
2,4-Distyrylpyridine	176	250/1 mm.			722
2,6-Distyrylpyridine	167.5		220		282,503
2,6-Distyryl-4-ethylpyridine	85		255		712
2,6-Distyryl-4-propylpyridine			215		454
2,6-Bis(*p*-methylstyryl)pyridine	202		226		709
2,6-Bis(*p*-hydroxystyryl)pyridine	254				118
2,6-Bis(3-hydroxy-4-methoxystyryl)-pyridine	147–48				452
2,4-Bis(3,4-methylenedioxystyryl)-pyridine	215				452

2,6-Bis(3,4-methylenedioxystyryl)-pyridine	195–96			452
2,4-Bis(*p*-methoxystyryl)pyridine	205			452
2,6-Bis(*p*-methoxystyryl)pyridine	183–86			452
2,6-Bis(*p*-methoxystyryl)-4-picoline	132–33			710
2,6-Bis(*p*-butoxystyryl)pyridine	168			715
2,6-Bis(*p*-acetoxystyryl)pyridine	183			118
2,6-Bis(3,4,5-trimethoxystyryl)pyridine	147–48		241	715
2,6-Bis(β-ethyl-*p*-hydroxystyryl)pyridine	282			118
2,6-Bis(α-ethyl-*p*-ethoxystyryl)pyridine		125/0.2 mm.		118
2,6-Bis(*p*-cyanostyryl)pyridine	175–76			118
2,4-Bis(*m*-nitrostyryl)pyridine	242–43			719
2,6-Bis(*o*-nitrostyryl)pyridine	140			498
2,6-Bis(*m*-nitrostyryl)pyridine	216			498
2,6-Bis(*p*-nitrostyryl)pyridine	258			498
2,6-Bis(*p*-aminostyryl)pyridine	230			118
2,6-Bis(*p*-dimethylaminostyryl)pyridine			318	717
2,4,6-Tristyrylpyridine	187–88	235–36		283
m-Bis[2-(2-pyridylethenyl)]benzene	121–22			493
p-Bis[2-(2-pyridylethenyl)]benzene	231.5–32			493
m-Bis[2-(4-pyridylethenyl)]benzene	211–12			493
p-Bis[2-(4-pyridylethenyl)]benzene	265–66			493
3,5-Diphenyl-2-stilbazole	144–45			741

TABLE V-11. Alkynyl and Aralkynylpyridines

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
3-Ethynylpyridine	38.5	83–84/30 mm.		467
2-(3-Butynyl)pyridine		40–42/0.5 mm.		440
2-Phenylethynylpyridine		152/1 mm.		507
4-Phenylethynylpyridine	95–95.5	109–10/0.5 mm.		447
6-Methyl-4-phenylethynylpyridine	45–45.5			545
2-(*p*-Chlorophenylethynyl)pyridine	99–100.5			447
4-(*p*-Chlorophenylethynyl)pyridine	119.5–22			447
2-(5-Chloro-2-hydroxyphenylethynyl)pyridine			194–95	546
2-(*o*-Nitrophenylethynyl)pyridine	54.5–55		175	317,547
2-(*m*-Nitrophenylethynyl)pyridine	93		199	317
2-(*p*-Nitrophenylethynyl)pyridine	157		206	317
2-(5-Chloro-2-nitrophenylethynyl)pyridine	128–29			546
2-(*o*-Aminophenylethynyl)pyridine	104–5			546
2-(2-Amino-5-chlorophenylethynyl)pyridine	130–31			546
2,6-Diphenylethynylpyridine	137–38			503
2,6-Bis(3,4,5-trimethoxyphenylethynyl)pyridine	133			715

TABLE V-12. Di- and Polypyridylalkanes and -alkenes

Compound	M.p., °C.	B.p., °C.	n_D^{20}	M.p. derivative, °C.	Ref.
2,2'-Methylenebipyridine		148–50/3–4 mm.	1.5772	dimethiodide 251	33
4,4'-Methylenebipyridine	138–40			di(methylbromide) 285–92	111
2,2'-Ethylenebipyridine	49.5–50.5	112–14/1–2 mm.		dipicrate 249.5–50	114,115
2,2'-Vinylenebipyridine	103–5	125–27/0.2 mm.			499
trans-2,2'-Vinylenebipyridine	119–20	145–54/1 mm.		methiodide 205–7	792
2,3'-Vinylenebipyridine	74			1-methiodide 185.5–86	430,723
4,4'-Ethylenebipyridine	114.5–16			dimethiodide 322	549
4,4'-Vinylenebipyridine	155.5–56.5			dimethiodide 235	549
2,2'-Trimethylenebipyridine		117/0.5 mm.	1.5607	dipicrate 208–9	519
4,4'-Trimethylenebipyridine	57–60			di(methylbromide) 212–21	111
2,2'-Propylidenebipyridine		125/0.2 mm.	1.5631	dipicrate 170.5–71	148
4,4'-Tetramethylenebipyridine	117–18.5				527
2,3-Bis(2-pyridyl)butane	134.4–34.8				95
2,2'-Pentamethylenebipyridine		153–54/1 mm.	1.5478^{25}	di(methylbromide) 199–203	111
4,4'-Pentamethylenebipyridine	56–58				111

(continued)

TABLE V-12. Di- and Polypyridylalkanes and -alkenes (*continued*)

Compound	M.p., °C.	B.p., °C.	$n_D^{t°}$	M.p. derivative, °C.	Ref.
2,2′-Hexamethylenebipyridine		160-65/0.5 mm.	1.5408^{25}	di(methylbromide). 225-28	111
4,4′-Hexamethylenebipyridine				di(methylbromide) 206-9	111
2,2′-Heptamethylenebipyridine		166-68/0.8 mm.	1.5379^{24}	di(methylbromide) 202-4	111
4,4′-Heptamethylenebipyridine				dihydrobromide 209-11	111
2,2′-Octamethylenebipyridine		177/0.6 mm.	1.5339^{26}	di(methylbromide) 200-1	111
4,4′-Octamethylenebipyridine				dihydrobromide 284-90	111
2,2′-Dodecamethylenebipyridine	42				110
α,α-Bis(2-pyridyl)toluene	83-84	170-76/0.01 mm.		dipicrate 169-70	47
1,2,3-Tris(4-pyridyl)propane	110-11			hydrochloride 230-32	76
1,2,3,4-Tetrakis(4-pyridyl)butane	262-65				76
2,2′,2″-Tripyridylmethane	100-1				147

TABLE V-13. Homoarylpyridines[a]

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
2-Phenylpyridine		270–72	176–77	563
3-Phenylpyridine		117-18/5 mm.	159–60	567,592
4-Phenylpyridine	77–78	274–75	195–96	563,730
4-Phenyl-2-picoline		280	210–13	552
5-Phenyl-2-picoline		143-45/13 mm.	189–90	741
6-Phenyl-2-picoline		117-20/4 mm.	129–30	736
6-Phenyl-3-picoline	137–39	241-45/2 mm.		64
6-Phenyl-4-picoline		110-15/3 mm.	185–87	736
2-(*m*-Tolyl)pyridine		106-7/2 mm.	175.5–77	461
2-(*p*-Tolyl)pyridine		108-9/4 mm.	180–80.5	461,554
4-(*p*-Tolyl)pyridine	90–91		199–201	731
6-Phenyl-2,4-lutidine		130-34/4 mm.	186–88	736
6-Phenyl-2,5-lutidine		287-88	179–80	737
4-Phenyl-2,6-lutidine	62–63.5	160-75/4 mm.	236–38	735,738
6-Phenyl-3,4-lutidine		146-50/6 mm.	202-3	736
2-Ethyl-5-phenyl-3-picoline		174-75/14 mm.	184–85	741
4-(*p*-*i*-Propylphenyl)pyridine	70–72		184–86	732
2-Nonyl-6-phenylpyridine		165-70/30 mm.		742
2,4-Diphenylpyridine	37–39	160-63/0.2 mm.	187–88	734
2,6-Diphenylpyridine	81–82		169	746
3,5-Diphenylpyridine	136–37		204.5-5.5	740
	194		276	551
3,5-Diphenyl-2-picoline	50–52	226-28/13 mm.	206-8	741
4,6-Diphenyl-2-picoline	73		213	734
2,6-Diphenyl-3-picoline		253-55/25 mm.		737
2,6-Diphenyl-4-picoline	73–74			739
2-Phenyl-6-(*p*-tolyl)pyridine	89		163	743

(*continued*)

TABLE V-13. Homoarylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
5-Benzyl-2-phenylpyridine	63–63.5		145–46	744
2,6-Diphenyl-3,5-lutidine	134–35			739
3,5-Diphenyl-2-ethylpyridine		230–31/14 mm.	190–91	741
4,6-Diphenyl-2-ethylpyridine			Nitrate: 180	745
5-Phenyl-2-stilbazole	137.5–38.5			741
2,6-Bis(*p*-tolyl)pyridine	162		174	743
4,6-Diphenyl-2-propylpyridine			Nitrate: 138	745
2,6-Diphenyl-3,4,5-collidine	116–17			739
3,5-Diphenyl-2-*i*-propylpyridine (?)	101–2		207–9	741
4,6-Bis(*p*-tolyl)-2-picoline	96		211	747
4,6-Diphenyl-2-*i*-butylpyridine			Nitrate: 124	745
2,6-Diphenyl-4-ethyl-3,5-lutidine	109–10			739
2,6-Diphenyl-4-propyl-3,5-lutidine	124–25			739
2,3,5-Triphenylpyridine (?)	123–24		232–34	741
2,4,6-Triphenylpyridine	137–38		193–94	735
2,4,6-Triphenyl-3-picoline	141–42		190–91	752
2,6-Bis(*p*-tolyl)-4-phenylpyridine	158–59		222	751
2,4,6-Triphenyl-3,5-lutidine	155–56		237–38	739
3,5-Diphenyl-2-stilbazole	144–45			741
2,3,4,6-Tetraphenylpyridine	182		192–93	593,748
2,3,5,6-Tetraphenylpyridine	233.5			750
2-(*p*-Tritylphenyl)pyridine	215			568
Pentaphenylpyridine	239–40		233–37	593,751
6-(*p*-Tolyl)-2,3,4,5-tetraphenylpyridine	238–38.5			733
2-(3-Biphenylyl)pyridine		75–85/0.002 mm.	169	565
3-(3-Biphenylyl)pyridine		75–85/0.002 mm.	178–79	565
4-(3-Biphenylyl)pyridine	81–82		231	565
2-(4-Biphenylyl)pyridine	141–42		186–87	565
3-(4-Biphenylyl)pyridine	151–52		208–10	565

4-(4-Biphenylyl)pyridine	209		215	565
2-(4-Biphenylyl)-4,6-diphenylpyridine	141		180	751
2-(1-Naphthyl)pyridine		161–64/1 mm.	199.5	591
x-(2-Naphthyl)pyridine	99–100		200	561
x-(2-Naphthyl)pyridine	69–70		179	561
x-(2-Naphthyl)pyridine			216	561
6-(1-Naphthyl)-2-phenylpyridine		190–92/12 mm.		743
2,4-Diphenyl-6-(2-napthyl)pyridine	124–25		233–34	751
4-(2-Acenaphthenyl)pyridine			264–65	577
2-(*p*-Chlorophenyl)pyridine	52–53		169–70	753
4-(*p*-Chlorophenyl)pyridine	70–71		225–27	753
2-(*p*-Bromophenyl)pyridine	62		168	753
4-(*p*-Bromophenyl)pyridine	129–31		213–14	753
2-(*p*-Iodophenyl)pyridine	85–86			753
4-(*p*-Chlorophenyl)-2,6-diphenylpyridine	128.5–30			735
2,6-Bis(*p*-chlorophenyl)-4-phenylpyridine	183		236	751
2,6-Bis(*p*-bromophenyl)-4-phenylpyridine	196		212	593
6-(*p*-Bromophenyl)-2,3,4-triphenylpyridine	172		226	593
6-(*m*-Bromophenyl)-2,3,4,5-tetraphenylpyridine	198–99			733
6-(*p*-Bromophenyl)-2,3,4,5-tetraphenylpyridine	256–57			733
2-(*o*-Hydroxyphenyl)pyridine	56	135–45/2 mm.	176–78	643,645
2-(*p*-Hydroxyphenyl)pyridine	159–60			753
3-(*m*-Hydroxyphenyl)pyridine	139			754
4-(*m*-Hydroxyphenyl)-2,6-lutidine	191			782
4-(*m*-Hydroxyphenyl)pyridine	227–28			585
2-(*o*-Methoxyphenyl)pyridine			155–56	758
2-(*m*-Methoxyphenyl)pyridine	95		154–56	758
2-(*p*-Methoxyphenyl)pyridine	49–50		192–93	758
3-(*o*-Methoxyphenyl)pyridine			182	758
3-(*m*-Methoxyphenyl)pyridine			160–62	585
4-(*o*-Methoxyphenyl)pyridine			205	758

(continued)

TABLE V-13. Homoarylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
4-(*m*-Methoxyphenyl)pyridine			203–4	758
4-(*p*-Methoxyphenyl)pyridine	95		205–6	758
2-(*p*-Ethoxyphenyl)pyridine	74–75		168–70	564
4-(*p*-Ethoxyphenyl)pyridine	100–1		199–200	753
3,5-Bis(3,4-dimethoxyphenyl)pyridine	173–74			740
p-(2-Pyridyl)benzaldehyde	55			554
p-(2-Pyridyl)benzoic acid	232			753
p-(2-Pyridyl)benzonitrile	97–98			753
Methyl *p*-(2-pyridyl)benzoate	90			753
3- or 6-(3-Pyridyl)salicylic acid	281			754
2-Hydroxy-4-(3-pyridyl)-*i*-phthalic acid	271			754
2-[2-Hydroxy-4,5,6-tris(carbomethoxy)-phenyl]pyridine	128			319
6-(*p*-Methoxyphenyl)-2-phenylpyridine	119			742
2,4-Diphenyl-6-(*p*-hydroxyphenyl)pyridine	189–90		243–34	751
2,6-Diphenyl-4-(*o*-hydroxyphenyl)pyridine	178			756
2,6-Diphenyl-4-(*p*-hydroxyphenyl)pyridine	214–15		219–20	751
2,4-Diphenyl-6-(*p*-methoxyphenyl)pyridine	100–2		210	751
2,6-Diphenyl-4-(*o*-methoxyphenyl)pyridine	119			755
2,6-Diphenyl-4-(*m*-methoxyphenyl)pyridine	123.5–24			735
2,6-Diphenyl-4-(*p*-methoxyphenyl)pyridine	100–1		192	751
2,4-Diphenyl-6-(4-hydroxy-3-methylphenyl)-pyridine	151		232	593
2,4-Diphenyl-6-(4-methoxy-3-methylphenyl)-pyridine	112		223	593
2,4-Bis(*p*-hydroxyphenyl)-6-phenylpyridine	222		245	751
2,6-Bis(*p*-hydroxyphenyl)-4-phenylpyridine	133–34		256	751
2,4-Bis(*p*-methoxyphenyl)-6-phenylpyridine	108–10		174–76	751

2,6-Bis(*p*-methoxyphenyl)-4-phenylpyridine	133–34	193–94	751
2,6-Diphenyl-4-(3,4-methylenedioxyphenyl)-pyridine	156		755
2,4,6-Tris(*p*-hydroxyphenyl)pyridine	282	293	751
2,4,6-Tris(*p*-methoxyphenyl)pyridine	133	196	751
2,6-Bis(*m*-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pyridine	105–6	166–68	757
2,6-Bis(*p*-methoxyphenyl)-4-phenyl-3,5-lutidine	167–68		739
2-(*p*-Methoxyphenyl)-3,4,5,6-tetraphenylpyridine	194–95		733
4-(3,4-Methylenedioxyphenyl)-2,3,5,6-tetraphenylpyridine	271		755
2-(2-Hydroxyacenaphthenyl)pyridine	126–27	170	577
x-(3,5-Dichloro-4-hydroxyphenyl)pyridine	225		572
x-(3,5-Dibromo-4-hydroxyphenyl)pyridine	226–28		572
2-(*o*-Nitrophenyl)pyridine	58–59	151–52	563
3-(*o*-Nitrophenyl)pyridine		182–83	563
4-(*o*-Nitrophenyl)pyridine	51–52	206–7	563,564
2-(*m*-Nitrophenyl)pyridine	74	157	563
3-(*m*-Nitrophenyl)pyridine	101–2	200–1	563
4-(*m*-Nitrophenyl)pyridine	109–10	250	563
2-(*p*-Nitrophenyl)pyridine	130.5–31.5	168	563,564
3-(*p*-Nitrophenyl)pyridine	148–49	220	563,564
4-(*p*-Nitrophenyl)pyridine	123–24	228–29	563,564
4-(*p*-Nitrophenyl)-2,6-lutidine	165–66		780
2,6-Bis(*p*-nitrophenyl)pyridine	293		563
2,4-Diphenyl-6-(*m*-nitrophenyl)pyridine	141–42	184	759
2,6-Diphenyl-4-(*m*-nitrophenyl)pyridine	150–51	188	759
2-(4-*t*-Butyl-3-nitrophenyl)pyridine (?)		160	585
3-(4-*t*-Butyl-3-nitrophenyl)pyridine (?)		217–18	585
4-(4-*t*-Butyl-3-nitrophenyl)pyridine (?)		231	585
x-(4-*t*-Butyl-2-nitrophenyl)pyridines	(mentioned; no data given)		585

(*continued*)

TABLE V-13. Homoarylpyridines (*continued*)

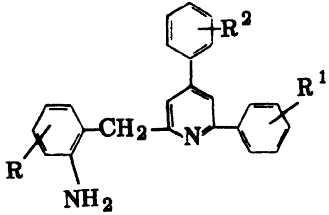
Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
1,3-Bis(x-pyridyl)-4-nitrobenzenes	(mixture)			588
1,4-Bis(x-pyridyl)-3-nitrobenzenes	(mixture)			588
2-(4-Hydroxy-3-nitrophenyl)pyridine	125			585
2-(2-Methoxy-4-nitrophenyl)pyridine	132–33		163–64	758
2-(2-Methoxy-5-nitrophenyl)pyridine	125–26			758
2-(3-Methoxy-2-nitrophenyl)pyridine (?)			155–56	585
2-(3-Methoxy-6-nitrophenyl)pyridine	76		190–91	585
2-(4-Methoxy-3-nitrophenyl)pyridine	85–86			758
3-(3-Methoxy-6-nitrophenyl)pyridine	91–92		202–4	585
x-(4-Hydroxy-2-methoxy-5-nitrophenyl)pyridine	320–22			572
2-(*o*-Aminophenyl)pyridine			185–86	760
2-(*m*-Aminophenyl)pyridine	70–72	213/20 mm.		565,762
2-(*p*-Aminophenyl)pyridine	97–98		218–19	564
3-(*o*-Aminophenyl)pyridine			155	760
3-(*m*-Aminophenyl)pyridine	77–78			565
3-(*p*-Aminophenyl)pyridine	102–4		185–88 219–20	564
4-(*m*-Aminophenyl)pyridine	165–66			565
4-(*p*-Aminophenyl)pyridine	232–34			564
4-(*p*-Dimethylaminophenyl)pyridine	234		246	573
4-(*p*-Ethylmethylaminophenyl)pyridine	154		216	573
4-(*p*-Diethylaminophenyl)pyridine	157		211	573
4-(*p*-Propylmethylaminophenyl)pyridine	123		200	573
4-(*p*-Butylmethylaminophenyl)pyridine	92			573
4-(*p*-Propylethylaminophenyl)pyridine	49			573
4-(*p*-Dipropylaminophenyl)pyridine	108		212	573
4-(*p*-Butylethylaminophenyl)pyridine	41			573
4-(*p*-*i*-Pentylmethylaminophenyl)pyridine	120			573
4-(*p*-Dibutylaminophenyl)pyridine	156–57		186–87	573

4-(*p*-Benzylmethylaminophenyl)pyridine	122		185	573
4-(*m*-Aminophenyl)-2,6-lutidine	117			761
4-(*p*-Aminophenyl)-2,6-lutidine	131			761
4-(2-Pyridyl)diphenylamine	133			589
4-(*m*-Aminophenyl)-2,6-diphenylpyridine	168–69		209	759
6-(*m*-Aminophenyl)-2,4-diphenylpyridine	151		207	759
4-(*p*-Dimethylaminophenyl)-2,6-diphenylpyridine	138			755
2-(*p*-Dimethylaminophenyl)-6-(2,5-dimethylpyrryl)-pyridine	185–86			557
2-[*p*-(2,5-Dimethylpyrryl)phenyl]pyridine	93–94	170–72/2 mm.		557
1,3-Bis(x-pyridyl)-4-aminobenzenes	(mixture; not separated.)			588
1,4-Bis(x-pyridyl)-3-aminobenzenes	(mixture; not separated.)			588
2-(*p*-Hydrazinophenyl)pyridine	117			564
3-(*p*-Hydrazinophenyl)pyridine	156–57			564
4-(*p*-Hydrazinophenyl)pyridine	205–7			564
4-(4-Amino-3,5-dibromophenyl)pyridine	136			573
2-(3-Amino-4-hydroxyphenyl)pyridine	166–67			585
2-(2-Amino-5-methoxyphenyl)pyridine			193–94	585
2-(3-Amino-4-methoxyphenyl)pyridine	98			585
2-(3-Amino-6-methoxyphenyl)pyridine	168–69			585
3-(2-Amino-5-methoxyphenyl)pyridine	131–32			585
4-(2-Pyridyl)diphenylamine-2′-carboxylic acid	198			589
4-(3-Pyridyl)diphenylamine-2′-carboxylic acid	248–50			589
2-(4-Amino-3-nitrophenyl)pyridine	148–49			588
3-(4-Amino-3-nitrophenyl)pyridine	176–77			585
2-(3,4-Diaminophenyl)pyridine	126–26.5			588
3-(3,4-Diaminophenyl)pyridine	122–23			585
3-(2-Hydrazino-5-methoxyphenyl)pyridine	(mentioned; no data given)			585
$3,5\text{-}Br_2\text{-}4\text{-}(p\text{-}Me_2NC_6H_4N:N)C_6H_2Py\text{-}4$	212			573
$2\text{-}(p\text{-}H_2NC_6H_4SO_2NH)C_6H_4Py\text{-}2$	200			762
$2\text{-}(p\text{-}H_2NC_6H_4SO_2NH)C_6H_4Py\text{-}3$	186–86.5			762

(continued)

TABLE V-13. Homoarylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
3-(*p*-$H_2NC_6H_4SO_2NH$)C_6H_4Py-2	170			762
4-(*p*-$H_2NC_6H_4SO_2NH$)C_6H_4Py-2	257.5			762
4-(*p*-$H_2NC_6H_4SO_2NH$)C_6H_4Py-4	217–18			762
4-(2-Pyridyl)-2′-sulfanilamidobiphenyl	164–65			762
4-(2-Pyridyl)-4′-sulfanilamidobiphenyl	298–99			762
4-(3-Sulfanilamidophenyl)-2,6-lutidine	269–70			762
4-(x-Pyridyl)-1-naphthol-2-sulfanilide	284–86			572
s-Bis[*p*-(2-pyridyl)phenyl]urea	278			585



R	R¹	R²		
H	4-MeO	4-MeO	137	763
4-Me	4-MeO	4-MeO	134	763
4-Br	4-MeO	4-MeO	158.5	763
H	4-Me	4-Me	126	763
3-Me	4-Me	4-Me	122	763
4-Me	4-Me	4-Me	152	763
4-Br	4-Me	4-Me	162	763
H	3-Me	3-Me	131	763
4-Me	3-Me	3-Me	140	763
H	4-Br	4-Br	164	763
4-Me	4-Br	4-Br	165	763
4-Br	4-Br	4-Br	156	763
H	3-Br	3-Br	139.5	763
H	4-Cl	4-Cl	150	763
4-Me	4-Cl	4-Cl	148	763
3-Me	4-Cl	4-Cl	160	763
H	3-Cl	3-Cl	134	763
4-Me	3-Cl	3-Cl	129	763

TABLE V-14. Heteroarylpyridines

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
2-(2-Pyridyl)quinoline	98		182–83	764
2-(3-Pyridyl)quinoline	66.5		199	764
2-(4-Pyridyl)quinoline	96		207	764
3-(2-Pyridyl)quinoline	101.5		227	587
3-(3-Pyridyl)quinoline	124		222–23	764
3-(4-Pyridyl)quinoline	124		213–14	765
4-(3-Pyridyl)quinoline	74	156–57/1 mm.	210–12	764
4-(4-Pyridyl)quinoline	83	152/0.1 mm.	225	764
5-(2-Pyridyl)quinoline	88–89		212	587
6-(2-Pyridyl)quinoline	82–83			587
6-(3-Pyridyl)quinoline	32–34		249–50	587
6-(4-Pyridyl)quinoline	104–5			587
7-(2-Pyridyl)quinoline	87–88		221	587
8-(2-Pyridyl)quinoline	74–76		209–10	587
8-(3-Pyridyl)quinoline	111–12		226	587
8-(4-Pyridyl)quinoline	127		238–40	587
2-(2,6-Dimethyl-4-pyridyl)quinoline	135		230	761
3-(2,6-Dimethyl-4-pyridyl)quinoline	100			761
4-(2,6-Dimethyl-4-pyridyl)quinoline	122			761
5-(2,6-Dimethyl-4-pyridyl)quinoline	151		231–34	761
6-(2,6-Dimethyl-3-pyridyl)quinoline	68		243	761
6-(2,6-Dimethyl-4-pyridyl)quinoline	84		224–25	761
7-(2,6-Dimethyl-4-pyridyl)quinoline	125			761
8-(2,6-Dimethyl-4-pyridyl)quinoline	132			761

1-(2-Pyridyl)isoquinoline	72		166–67	635
1-(4-Methyl-2-pyridyl)isoquinoline	55.2–55.8		161–61.5	630
1-(3-Methyl-2-pyridyl)isoquinoline		165/0.35 mm.	156–56.5	630
1-(2-Pyridyl)acridine	111.5			589
3-(2-Pyridyl)acridine	140			589
3-(3-Pyridyl)acridine	132			589
3-(4-Pyridyl)acridine	179			589
5-(3-Pyridyl)acridine	118			589
4-(2-Pyridyl)cinnoline	128–29		201–3	260
4-(3-Pyridyl)cinnoline	141			532
4-(4-Pyridyl)cinnoline			276–78	532
6-(2-Pyridyl)quinoxaline	144–45			585
3-Methyl-2-(2-pyridyl)indole	104–5		206–7	105
3-Ethyl-2-(2-pyridyl)indole	75–76		205	105
3-Ethyl-2-(4,5-diethyl-2-pyridyl)indole	110–11	200–10/0.4 mm.	218–21	458
2-(2-Pyrryl)pyridine	90		222.5–23	773,774
3-(2-Pyrryl)pyridine	100–2		202–3	775
2-(3-Pyrryl)pyridine	132		211	773
2,5-Bis(2-pyridyl)pyrrole	(mentioned; no data given)			772
2-(2-Pyridyl)imidazoline	97–98			766
2,4-Diphenyl-6-(3-indazolyl)pyridine	228			768
4-(2-Pyridyl)-4H-1,2,4-triazoline	169			767
4-(3-Pyridyl)-4H-1,2,4-triazoline	162			767
2-(2-Pyridyl)benzimidazole	220–21			766
2-(4-Pyridyl)benzimidazole	217–18			769
5-(2-Pyridyl)tetrazole	217–19			770

(continued)

TABLE V-14. Heteroarylpyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
5-(3-Pyridyl)tetrazole	245–47			770
5-(4-Pyridyl)tetrazole	268–69			770
2-(3-Pyridyl)oxazoline	71			771
2-(4-Pyridyl)oxazoline	117			771
2-(2-Pyridyl)benzoxazole	(mentioned; no data given)			766
2-(2-Pyridyl)thiazole	46–46.3			630
4-(2-Pyridyl)thiazole	103–103.5			630
2-(2-Pyridyl)benzothiazole	133–33.5			224
2-(4-Pyridyl)benzothiazole	134–35			226
2-(2-Pyridyl)naphthothiazole	137–38			224
2-(2-Pyridyl)selenonaphthene	142			502
2-(4-Pyridyl)selenonaphthene	187			502
6-(2-Pyridyl)-8-(x-pyridyl)quinolines	118–21	mixture—not separated		588
2,6-Bis(2-quinolyl)-4-phenylpyridine	295–96			603
2,3,4,5-Tetrakis(4-pyridyl)thiophene	251.5–52.5			76
2,6-Bis(4-4H-1,2,4-triazolyl)pyridine	325–27			767
2,5-Bis(4-pyridyl)-1,3,4-thiadiazole	242			749

TABLE V-15. Bi- and Polypyridines

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
2,2′-Bipyridine	70.1	273–75	157–58.5	601
2,3′-Bipyridine		294–95	151–52	644,595
2,4′-Bipyridine	61.1–61.5		215–16	623
3,3′-Bipyridine	68	291-92/736 mm.	232	729
3,4′-Bipyridine (?)			199–201	623
4,4′-Bipyridine	114	305	262	597,614
$[\mathrm{C}^{14}]$-2,2′-Bipyridine	69–70			655
2-Methyl-4,4′-bipyridine	94			725
3,3′-Dimethyl-2,2′-bipyridine		293–98	188–89	602
4,4′-Dimethyl-2,2′-bipyridine	171–72			602
5,5′-Dimethyl-2,2′-bipyridine	(mentioned; no data given)			602
6,6′-Dimethyl-2,2′-bipyridine	89.5–90.5		170–71	604
2,2′-Dimethyl-4,4′-bipyridine	84		240	725
3,3′-Dimethyl-4,4′-bipyridine	125	293	230	727
4,4′-Dimethyl-x,x′-bipyridine			194	697
6,6′-Dimethyl-x,x′-bipyridine		270–71		726
4,4′-Diethyl-2,2′-bipyridine	38–40	147–50/0.3 mm.		603,613
4,4′,6,6′-Tetramethyl-2,2′-bipyridine	144–45	150/4–5 mm.	200–20 dec.	791
2,2′,6,6′-Tetramethyl-4,4′-bipyridine	148–49		273	728
2,2′,6,6′-Tetramethyl-3,3′-bipyridine	55			726
2,2′,4,4′,6,6′-Hexamethyl-3,3′-bipyridine	66–69	291–92		598
6-Phenyl-2,2′-bipyridine	83.5–4.5	145–55/0.2 mm.	173.8–74.0	630
4,4′-Diphenyl-2,2′-bipyridine	187–88			603
6,6′-Diphenyl-2,2′-bipyridine	176–78			643
6,6′-Bis(o-hydroxyphenyl)-2,2′-bipyridine	102.5–3.5		193.5–95	643
6,6′-Bis(o-methoxyphenyl)-2,2′-bipyridine		190-95/2 mm.	211–12	643
2,2′,6′,2″-Tripyridine	84–85	370	206	609

(continued)

TABLE V-15. Bi- and Polypyridines (*continued*)

Compound	M.p., °C.	B.p., °C.	M.p. picrate, °C.	Ref.
3,3′,5′,3″-Tripyridine	249			724
2,4-Bis(3-pyridyl)pyridine	(mentioned; no data given)			621
2,6-Bis (3-pyridyl)pyridine	(mentioned; no data given)			621
2,6-Bis(2-pyridyl)-4-phenylpyridine	208			619
2,6-Bis(3-pyridyl)-4-phenylpyridine	221–22			619
2,6-Bis(4-methyl-2-pyridyl)-4-phenylpyridine	228–29			603
2,6-Bis(4-ethyl-2-pyridyl)-4-phenylpyridine	114–15			603
4,4′,4″-Triphenyl-2,2′,6′,2″-tripyridine	257–58			603
6,4′,6″-Triphenyl-2,2′,6′,2″-tripyridine	190–91			603
2,6-Bis(3-pyridyl)-3,4,5-triphenylpyridine	278–79			619
3,5-Bis(2-pyridyl)-2,4,6-triphenylpyridine	280–81			619
6,6′-Bis(2-pyridyl)-2,2′-bipyridine	219–20		312	606
5,5′-Bis(3-pyridyl)-3,3′-bipyridine	290			724
2,4,6-Tris(3-pyridyl)pyridine	273.5–74.5			619
2,6-Bis[6-(2-pyridyl)-2-pyridyl]pyridine	265			606
3,5-Bis[5-(3-pyridyl)-3-pyridyl]pyridine	330			724
2,6-Bis(3-pyridyl)-3,5-bis(2-pyridyl)-4-phenylpyridine	277–78			619
6,6′-Bis[6-(2-pyridyl)-2-pyridyl]-2,2′-bipyridine	350			606

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CHAPTER VI

Halopyridines

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A. INTRODUCTION

All of the monohalopyridines are now known. Most of the possible polychloro- and polybromopyridines, and a very great variety of substituted halopyridines, have been prepared.

Pyridine may be halogenated directly. It is less reactive than benzene in substitutions of this type, although the ready formation of molecular addition compounds with halogen complicates a direct comparison. The displacements of hydroxyl in 2- and 4-pyridinols and of amino by diazotization of aminopyridines stand as preparative methods of primary importance. A rather wide variety of other methods have also been used to prepare substituted halopyridines.

Halopyridines undergo most of the reactions known for halobenzenes, as well as several others. The 2 and 4 halogens are generally more reactive than that of halobenzene, while the 3 halogen is of about the same order of reactivity. The halopyridines are important as reactive intermediates in synthetic sequences, and as such have been widely employed. While some halo derivatives of the dietary factors and medicinal compounds derived from pyridine have been prepared and studied, the halopyridines are not of great utility *per se*.

Side-chain halogen derivatives of pyridine are prepared by standard techniques applicable to the preparation of haloalkylamines. The effect of the pyridine ring is noted primarily in its activation of halogen on the carbon atom attached to the ring. The tendency toward formation of quaternary pyridinium salts with the side-chain halogen is, of course, ever present.

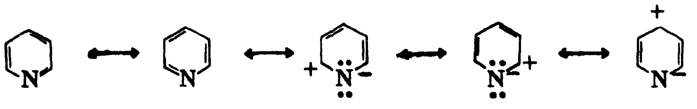
B. NUCLEAR HALOGEN DERIVATIVES

1. Preparation

a. Direct Halogenation

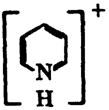
(a) Introduction. Replacement of hydrogen by halogen in the pyridine nucleus has been achieved by several methods. Direct halogenation of unsubstituted pyridine does not occur at room temperature. Pyridine may be halogenated directly at elevated temperatures, frequently better in the presence of a catalyst. High temperature bromination of pyridine has been studied rather extensively. Halogenation of pyridine salts has also been found possible, but again only at high temperatures.

The relative unreactivity of pyridine toward electrophilic reagents such as halogen, as compared to benzene, may be explained satisfactorily by considering the resonating system which constitutes the pyridine molecule. The electron-attracting power of the nitrogen atom leads to significant contributions from such activated states as VI-3, VI-4, and VI-5. even though VI-1 and VI-2 are considered

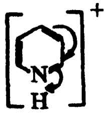


(VI-1) (VI-2) (VI-3) (VI-4) (VI-5)

to be the major contributing states. Similar considerations apply to the reactivity of the pyridinium ion toward halogen. In this case electron density will be even more reduced at positions 2 and 4 by the strong electron-attracting capacity of the positively charged nitrogen atom. With the tendency for electron shift as indicated in VI-7,



(VI-6)



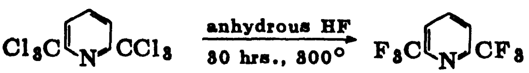
(VI-7)

the relative contribution of the polarized forms corresponding to VI-3, VI-4, and VI-5 will be even greater for the pyridinium ion. Accordingly, it is not surprising to find that the pyridinium ion halogenates at position 3, which is relatively less affected by the electron shift toward nitrogen.

The course of halogenation of substituted pyridines depends upon the nature of the substituent. In general, when only meta-directing groups are present the pyridine nucleus cannot be halogenated. Ortho- and para-directing groups facilitate substitution; their influence is discussed more fully below.

(b) Fluorination. The direct fluorination of pyridine has not been studied extensively. Pyridine and fluorine in the presence of copper (plated) or cobalt trifluoride give some perfluoropiperidine, but mostly products of ring opening and general decomposition (*1*). The fluorination of picolines and lutidines has also been studied (*2*). Fluorine and lutidine in the presence of gold- or silver-plated copper or with cobalt trifluoride give about 5% of the completely or almost completely fluorinated derivative (*3*). Again the low yield is attributable to decomposition, ring opening, and incomplete fluorination.

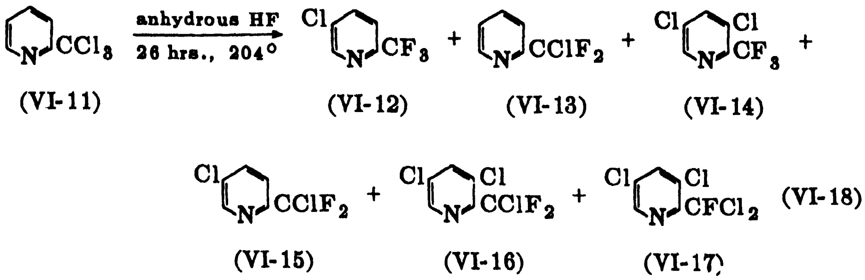
Treatment of trichloromethylpyridines with anhydrous hydrogen fluoride at elevated temperatures results in replacement of the chlorine by fluorine (VI-10) (*4*). Nuclear chlorination may accompany



(VI-10)

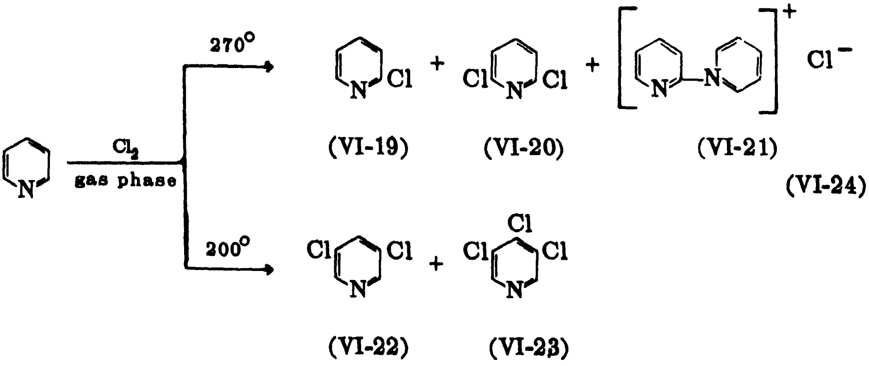
(VI-8) (VI-9)

the substitution (VI-18). Reactions of this sort do not take place with antimony trifluoride at atmospheric pressure. Decomposition of the molecular addition compound of pyridine and fluorine leads to nuclear fluorination (see later).

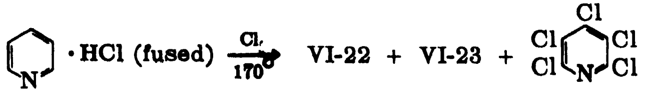


(VI-11) (VI-12) (VI-13) (VI-14) (VI-15) (VI-16) (VI-17) (VI-18)

(c) **Chlorination.** (*1*) *Pyridine and Alkylpyridines.* The gas phase chlorination of pyridine has been studied by Wibaut (*5*). The position substituted varies with the temperature (VI-24), although less widely than in bromination. The presence of 1-(2-pyridyl)pyridinium chloride (VI-21) is indicated by the isolation of 2-aminopyridine from the reaction products upon hydrolysis. To effect 3- or 3,5-substitution the reaction must be carried out at 200°; it proceeds sluggishly at this temperature. At 400° much carbonization occurs, and the main product is 2,6-dichloropyridine (VI-20). Fused pyridine hydrochloride at 170° gives a considerable amount of VI-22,



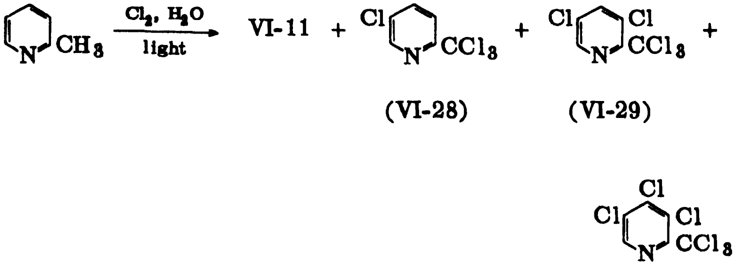
(VI-19) (VI-20) (VI-21) (VI-22) (VI-23) (VI-24) along with smaller amounts of polychlorinated derivatives (VI-27) (*5*).



(VI-27)

(VI-25) (VI-26)

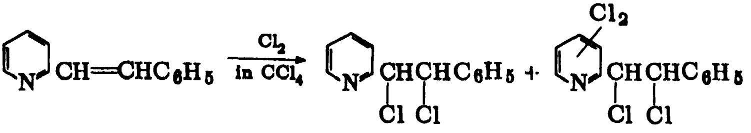
Following the early investigations of Sell (*6*) and of Seyfferth (*7*), the chlorination of picolines has been studied by McBee *et al.* (*8*). Substitution of the side chain takes place first, but if sufficiently vigorous conditions are employed, chlorine is introduced into the nucleus (VI-31). The structures of these products were determined by hydrolysis to the corresponding picolinic acids. A similar instance of nuclear chlorination, following addition to an unsaturated side chain, has been reported (VI-35) (*9*). The thermal decomposition of pyridine hydrochloride perchloride leads to nuclear chlorinated products (see later). Somewhat analogous to this is the pro-



(VI-28) (VI-29)

(VI-31)

(VI-30)



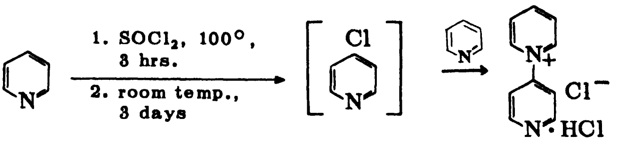
(VI-35)

(VI-32) (VI-33) (VI-34)

cedure of Sell and Dootson (*10*), wherein a solution of pyridine saturated with hydrochloric acid is treated with chlorine for a period of one week, forming 3,5-dichloropyridine along with the main product, 2,3,4,6-tetrachloropyridine.

When pyridine is heated with excess phosphorus pentachloride at 210–220° or at 270–280° (*11,12*), a mixture of di-, tri-, tetra-, and pentachloropyridines is obtained. From this mixture 3,5-dichloropyridine, 2,3,5-trichloropyridine, two other trichloropyridines of m.p. 67–68° and 71–72°, 2,3,4,6-tetrachloropyridine, 2,3,4,5-tetrachloropyridine, and pentachloropyridine have been isolated (*12*).

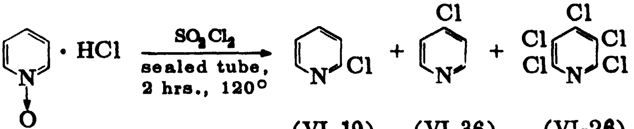
The formation of 1-(4-pyridyl)pyridinium chloride hydrochloride (VI-37) from pyridine and thionyl chloride (*13*) suggests the intermediate formation of 4-chloropyridine (VI-36).



(VI-38)

(VI-36) (VI-37)

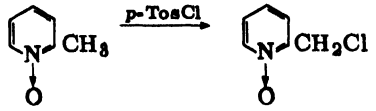
(*2*) *Pyridine 1-Oxides.* (*Cf.* Chapter IV, p. 121.) The reaction of pyridine 1-oxides with chlorine has apparently not been reported (*14*), but other chlorinating agents give rise to otherwise difficultly available chloropyridines. Thus, Bobranski and co-workers (*15*) report that pyridine 1-oxide and sulfuryl chloride (VI-39)



(VI-39)

(VI-19) (VI-36) (VI-26)

give a 65% yield of a mixture comprising 57% of VI-19, 43% of VI-36, and a small amount of VI-26. With phosphorus pentachloride, pyridine 1-oxide is said (*16*) to lead to VI-36. Similarly, 2,6-lutidine 1-oxide is converted by phosphorus oxychloride to 4-chloro-2,6-lutidine (*17*). By contrast, however, 2-picoline 1-oxide is transformed by *p*-toluenesulfonyl chloride to 2-chloromethylpyridine 1-oxide (VI-40), retaining the oxide function (*18*). This type of

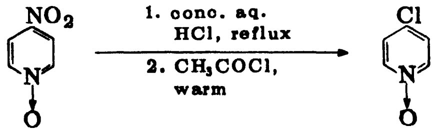


(VI-41)

(VI-40)

reaction has been extended to include substituted pyridine 1-oxides. From 3-bromopyridine 1-oxide (readily prepared by per-acid oxidation of 3-bromopyridine) is obtained a mixture containing 3-bromo-4-chloro-, 3-bromo-2-chloro-, and 3-bromo-6-chloropyridines (*19*). The isomer with chlorine at position 4 is the most abundant, but the combined substitution at the 2 and 6 positions exceeds that at 4.

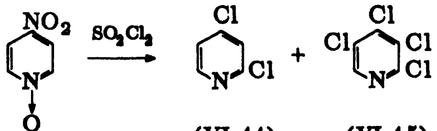
Since 4-nitropyridine 1-oxide is readily available from pyridine 1-oxide by nitration (*20–22*), it serves as an interesting starting material for the preparation of halopyridines. With aqueous hydrogen chloride at reflux, the nitro group is replaced and the oxide function retained (VI-43), giving 4-chloropyridine 1-oxide in 80% yield (*23*). A yield of 90% may be had by warming the nitro oxide with acetyl chloride (*24*). A discrepancy in the melting point of VI-42 pre-



(VI-43)

(VI-42)

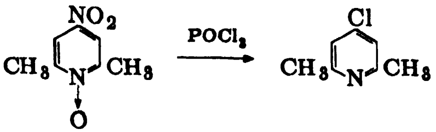
pared by these two methods has been shown to be due to polymorphism (*25*). The oxide function is lost when 4-nitropyridine 1-oxide is heated with sulfuryl chloride (*26,27*). The main product is 2,4-dichloropyridine (VI-44), but 4-amino-2,3,5-trichloropyridine may be obtained by treating the residue with ammonia, indicating the pres-



(VI-46)

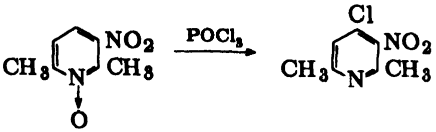
(VI-44) (VI-45)

ence of 2,3,4,5-tetrachloropyridine (VI-45). The reaction of 4-nitropyridine 1-oxide with phosphorus oxychloride at 70° leads mainly to VI-42, but under more vigorous conditions VI-44 is the main product (*23*). The nucleophilic displacement of the nitro group of pyridine 1-oxides seems to be limited to the 4 position. The displacement of the 4-nitro group contrasts with retention of the 3-nitro group during chlorination at the open 4 position (VI-48, VI-50) (*28*).



(VI-48)

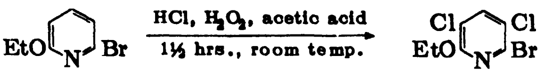
(VI-47)



(VI-50)

(VI-49)

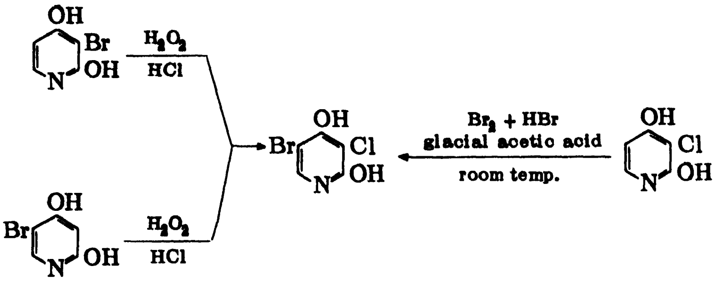
(*3*) *Substituted Pyridines.* Direct halogenation of the pyridine nucleus is often facilitated by the presence of an activating group. When 2-bromo-6-ethoxypyridine is treated with hydrochloric acid and hydrogen peroxide in acetic acid, two atoms of chlorine are introduced to form 2-bromo-3,5-dichloro-6-ethoxypyridine (VI-52)



(VI-52)

(VI-51)

(*29*). In a similar manner 3,5,6-trichloro-2-pyridinol is obtained from 6-chloro-2-pyridinol (*29*). Gaseous chlorine may be used rather than the *in situ* generation; thus 4-chloro-2-ethoxypyridine is transformed to 4,5-dichloro-2-ethoxypyridine (*26*). The hydrogen chloride–hydrogen peroxide halogenation has been extended to other hydroxypyridines (VI-53), and is said to give good yields of isomer-free products (*31*). In the case of 3-bromo-2,4-pyridinediol the bromine appears to migrate to a less hindered position under the con-



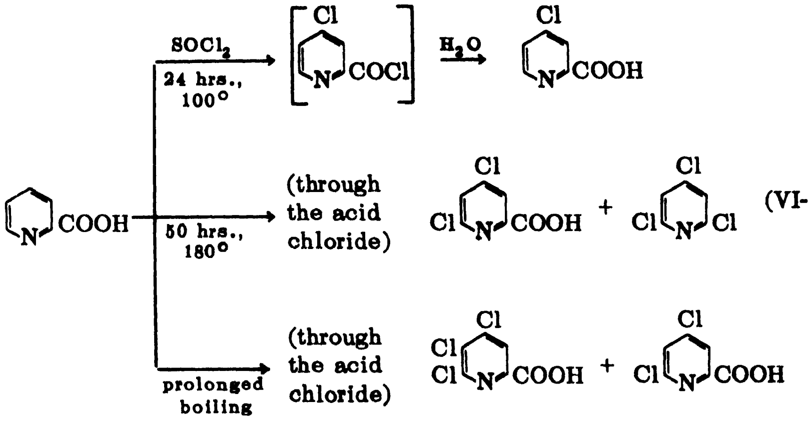
(VI-53)

ditions of the reaction (VI-53). The rearrangement seems to be an intramolecular process.

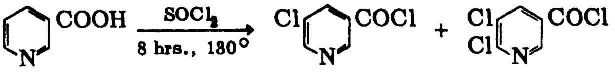
Both 4-hydroxypicolinic acid (*32*) and 4-chloro-6-hydroxypicolinic acid (*33*) chlorinate in the 3 and 5 positions in alkaline solutions.

2-Aminopyridine chlorinates readily either in ethanol at 0° (*34*), or in 25% sulfuric acid (*35*). The yield in either case seems to be about the same. The product, which is obtained in 80% yield, is comprised of about 65% of 2-amino-5-chloropyridine, while most of the remainder is 2-amino-3,5-dichloropyridine. A better yield of the dichloroaminopyridine may be obtained by chlorinating the monochloro compound under the same conditions (*34*). An amino group in position 4 activates the ring sufficiently to permit polyhalogenation (*31*). The activating effect of the amino group, even when opposed by a nitro group, is illustrated by the chlorination of 6-amino-3-nitro-2-picoline to form 6-amino-5-chloro-3-nitro-2-picoline (*36*).

All three pyridinemonocarboxylic acids are halogenated by prolonged treatment with thionyl chloride. These reactions are among the few examples of halogenation of a pyridine nucleus substituted by a meta-directing group. Picolinic acid gives the 4-chloro derivative in twenty hours at 100°; under more severe conditions polyhalogenation occurs (*37*) (VI-54). Graf (*38*) has observed that a lower proportion of thionyl chloride favors trisubstitution, owing to the higher boiling point of the reaction mixture. Nicotinic acid (*37*), or its hydrochloride (*39*), gives a mixture of the 5-chloro and 5,6-dichloro derivatives in eight hours at 130°. Here, however, reduced proportions of thionyl chloride favor *mono*substitution. Isonicotinic acid gives a mixture of 3-chloro (VI-58) and 3,5-dichloro



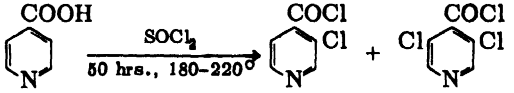
(VI-54)



(VI-57)

(VI-55) (VI-56)

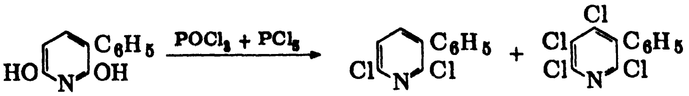
(VI-59) derivatives when treated with thionyl chloride (*37*). (*Cf.* Chapter X.)



(VI-60)

(VI-58) (VI-59)

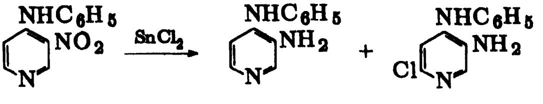
Nuclear substitution sometimes takes place as a side reaction in the course of transformations of pyridine derivatives. Thus 2,4,5,6-tetrachloro-3-phenylpyridine (VI-62) is formed in addition to the expected 2,6-dichloro-3-phenylpyridine (VI-61) when 3-phenyl-2,6-pyridinediol is treated with phosphorus oxychloride and phosphorus



(VI-63)

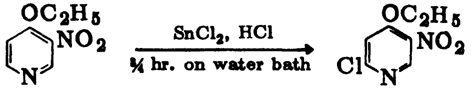
(VI-61) (VI-62)

pentachloride (*40*). With phosphorus pentachloride (*41,42*) 1-methyl-2(1*H*)-pyridone leads not only to 2-chloropyridine but also to 2,5-dichloropyridine. An atom of chlorine enters the nucleus at position 6 during the course of reduction of 4-anilino-3-nitropyridine with stannous chloride (VI-65) (*43*). A somewhat similar chlorination is noted (*44*) when 4-ethoxy-3-nitropyridine is treated with stannous chloride and hydrochloric acid (VI-67). Bremer (*45*) has reported that chlorine is introduced ortho to the nitro (resulting amino) group of 4-butylamino-3-nitropyridine when it is treated with the same reagents. Likewise 3-amino-4-butylamino-2,5-dichloropyridine and 3-amino-5-bromo-4-butylamino-2-chloropyridine are formed from the corresponding 5-chloro and 5-bromo analogues.



(VI-65)

(VI-64)



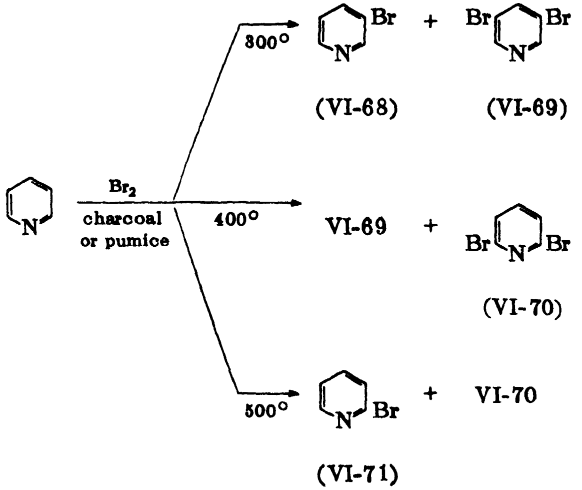
(VI-67)

(VI-66)

(d) Bromination. When pyridine or its salts are treated with bromine in the cold or at room temperature, molecular addition products are formed. These products are discussed more fully later.

At higher temperatures bromine may be introduced into the nucleus. This was first described by Hoffman (*46,47*) who treated pyridine hydrochloride with bromine in a sealed tube at 200° to obtain 3-bromopyridine and 3,5-dibromopyridine, along with unreacted pyridine. The combined yield of the two products was 27% (*48*). Blau (*49*) reports that bromination can be accomplished without using a sealed tube by passing a stream of bromine vapor in carbon dioxide through a melt of pyridine hydrochloride under reflux or by the dropwise addition of bromine to the stirred melt. Improvements in these earlier procedures by the use of iron (*50*) and mercuric chloride (*51*) have been described with yields increased up to about 40%. A tribromopyridine of m.p. 89–90° (all possible tribromopyridines are known; none melts at this temperature) is described as the product resulting from the bromination of pyridine hydrochloride with bromine in the presence of hypobromite (*52*).

More recently the vapor phase bromination of pyridine has been studied rather extensively by den Hertog and Wibaut (*53–56*), with improvements by McElvain and Goese (*57*). At 300° the main products are 3-bromopyridine (VI-68) and 3,5-dibromopyridine (VI-69). At 400° a mixture of products results from which both VI-69 and 2,6-dibromopyridine (VI-70) may be isolated. When the temperature is further increased to 500°, pyridine is smoothly brominated to a mixture of 2-bromopyridine (VI-71) and VI-70; this reaction made VI-71 readily accessible for the first time.



(VI-72)

A complete investigation of the gas phase bromination at 300° shows that while the main products are those indicated, other positions also are substituted (*53*). The product contains VI-68, VI-69, 2,3-dibromopyridine, 2,5-dibromopyridine, 2,6-bromopyridine, 3,4,5-tribromopyridine, and 2,3,5-tribromopyridine, but no 2,4-dibromopyridine. The 3-bromo- and 3,5-dibromopyridines may be isolated with reasonable ease.

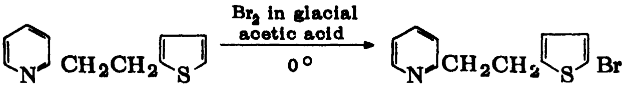
The preparative utility of the gas phase bromination is discussed by McElvain and Goese (*57*), who report that the reaction is slow at both 300° and 500°, but faster and more practical at the higher temperature. The 300° reaction suffers from the further disadvantage of periodic clogging of the reaction tube with decomposition products. The low yield of 4-bromo derivatives is probably due to their instability. Wheland (*58*) has suggested that a free radical mechanism predominates at 500° and a nucleophilic displacement process at 300°.

Under the same gas phase conditions, 2-bromopyridine gives a mixture containing 2,3,5-tribromopyridine, 2,6-dibromopyridine, 3,5-dibromopyridine, 3-bromopyridine, 2,3,4,5-tetrabromopyridine, and pentabromopyridine (*59*). Halogen migration evidently occurs. 3-Bromopyridine gives similar products, while 4-bromopyridine gives a fair yield of 2,4,6-tribromopyridine (*21*). 2,6-Dibromopyridine gives a mixture of 2,3,6-tribromopyridine, 2,4,6-tribromopyridine, and 2,3,5,6-tetrabromopyridine (*21,60*). From 3,5-dibromopyridine are obtained 2,3,5-tribromo- and 2,3,5,6-tetrabromopyridines. The completely brominated pentabromopyridine is formed along with 2,3,4,5-tetrabromopyridine upon brominating 3,4,6-tribromopyridine. Similarly, further bromination of 3,4-dibromopyridine (a minor by-product from the 300° reaction) leads to 2,6-dibromopyridine, 2,4,5-tribromopyridine, 2,3,4-tribromopyridine, and 2,3,4,6-tetrabromopyridine. Some 2-bromopyridine was known to be in the starting material, but the formation of 2,6-dibromopyridine may equally well represent halogen migration. The stepwise bromination of 3-bromopyridine to 3,5-dibromopyridine is the subject of an early paper (*61*), in which the melted salt bromination technique is employed.

4-Bromopyridine may be obtained in a manner analogous to that used to prepare 4-chloropyridine by treating 1-(4-pyridyl)pyridinium bromide with hydrogen bromide at elevated temperatures (*62*). The reaction of pyridine with *N*-bromosuccinimide, catalyzed by aluminum chloride in carbon tetrachloride, leads to 3,5-dibromopyridine in unstated yield (*63*).

A product of m.p. 68–69°, which analyzes correctly for a tribromopicoline but which does not hydrolyze to give isonicotinic acid, is formed when 4-picoline is brominated in glacial acetic acid containing sodium acetate (*64*). 2-Picoline hydrochloride and bromine give a perbromide which decomposes upon heating to form a monobromopicoline (*57*). Other experiments with 2-picoline have led only to polymeric products. A bromo-3-picolyl hydrobromide dibromide is said to result when 3-picoline is treated with bromine in carbon tetrachloride (*65*). A more detailed description of the use of bromine molecular addition compounds in the synthesis of bromopyridines is described in a later section (p. 336).

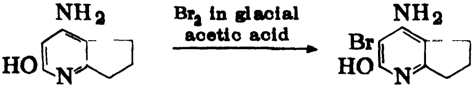
Equation VI-74 illustrates the inertness of pyridine toward halogenation as compared to thiophene (*66*).



(VI-74)

(VI-73)

Polybromo derivatives are readily formed from pyridinols and their *O*- and *N*-alkyl derivatives. Thus 2,4,6-tribromo-3-pyridinol may be obtained by treating 3-pyridinol, 2-bromo-3-pyridinol, or 6-bromo-3-pyridinol with bromine water (*67*), while 2,4,5,6-tetrabromo-3-pyridinol is formed similarly from 5-bromo-3-pyridinol. This type of bromination has been extended to more complex derivatives of pyridine, as indicated in the preparation of 4-amino-3-bromo-6,7-dihydro-5*H*,1-pyrindin-2-ol (VI-75) (*69*). *N*-Bromosuccinimide reacts with 6-methyl-2-pyridinol to give 3,5-dibromo-6-methyl-2-pyridinol (*70*). 2,4-Pyridinediol is readily brominated in the 3 position in acidic solution at 0° (*53*). At room temperature 3,5-dibromination occurs. 5-Chloro-2,4-pyridinediol brominates in the 3 position at 100° (*26*). At higher temperatures the hydroxyl groups may be replaced, as in the bromination of 2,4-pyridinediol at 500° to give 2,3,4-tribromopyridine. This is said to be the best preparative method for the latter compound (*53*).

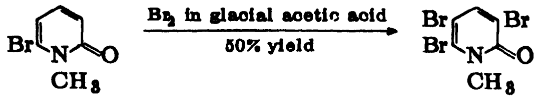


(VI-76)

(VI-75)

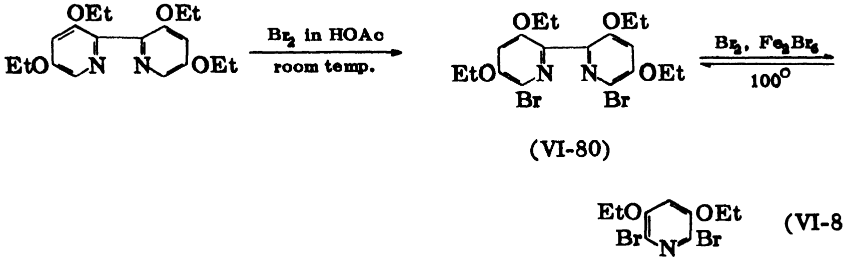
2,6-Dibromo-4-methoxypyridine treated with bromine at 160° for forty-eight hours gives 2,3,5,6-tetrabromo-4-pyridinol (*71*). Ether cleavage is caused by the hydrogen bromide liberated during the reaction. The same product is formed by bromination of 2,6-dibromo-4-pyridinol. 5-Bromo-3-ethoxypyridine takes up two additional atoms of bromine at 100° to form 2,5,6-tribromo-3-ethoxypyridine (*29*).

Bromine in sulfuric acid solution is used to brominate 1-alkylpyridones. Thus 3-(or 5-)bromo-1-methyl-2(1*H*)-pyridone give 3,5-dibromo-1-methyl-2(1*H*)-pyridone (*72*). Bromine in acetic acid also may be used, as in the preparation of 3,5,6-tribromo-1-methyl-2(1*H*)-pyridone (VI-78) (*73*). The bromine must all be added at one time



(VI-77) (VI-78) (VI-79)

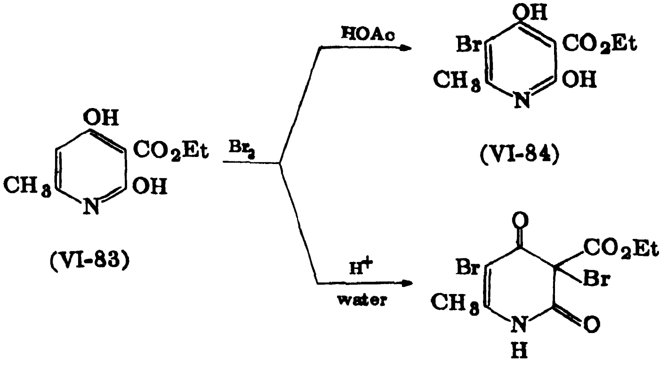
or a product of unknown structure, m.p. 188° (dec.), results. Cleavage of a carbon-carbon bond between two pyridine rings, with bromination at the points of rupture, results when 6,6′-dibromo-3,3′,5,5′-tetraethoxy-2,2′-bipyridine (VI-80) is heated with ferric bromide and bromine (*74*). This is an equilibrium process, however, and the equilibrium lies largely toward the starting bipyridine.



(VI-80)

(VI-81) (VI-82)

The activating effect of an hydroxyl group in the presence of a carboxyl group is seen in the bromination of 4-hydroxypicolinic acid to 3,5-dibromo-4-hydroxypicolinic acid in quantitative yield (*32*). Similarly 4,6-dihydroxynicotinic acid and ethyl 2,4-dihydroxy-6-methylnicotinate (VI-83) are readily brominated in the 5 position in glacial acetic acid (*53,75*). Polarity of the solvent does not seem to be important, since ethyl 6-hydroxy-2-methylnicotinate also brominates in the 5 position in carbon tetrachloride solution (*79*). Bromine in acidic aqueous solution, on the other hand, converts VI-83 to an oxidized dibromo derivative (VI-85). 3-Carbamoyl-4,6-dimethyl-2-pyridinol brominates in acetic acid to give the 5-bromo derivative (*76*). Reduction of the carbamoyl group to aminomethyl prior to bromination does not alter the course of the reaction, and the analogous 3-aminomethyl-5-bromo-4,6-dimethyl-2-pyridinol is formed. Quite analogously, ethyl 4-ethoxyethyl-2-hydroxy-6-methylnicotinate and the corresponding amide may be brominated in acetic acid to the 5-bromo derivatives (*77*). 5-Benzoyl-2-pyridinol may be brominated in methanol to produce 5-benzoyl-3-bromo-1-methyl-2(1*H*)-pyridone (*78*).

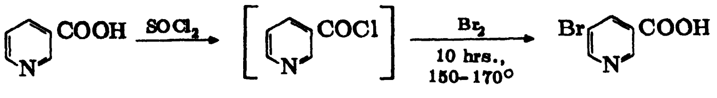


(VI-85)

(VI-86)

The deactivating influence of a nitro group may also be overcome, as seen in the bromination of 3-nitro-4-pyridinol in the 5 position in aqueous solution, and also in the bromination of 4,6-dimethyl-5-nitro-2-pyridinol and 3-nitro-2,4-pyridinediol in acetic acid to obtain 3-bromo-4,6-dimethyl-5-nitro-2-pyridinol and 5-bromo-3-nitro-2,4-pyridinediol, respectively (*80,81*).

Paralleling the nuclear chlorination of pyridinecarboxylic acids by thionyl chloride is the nuclear bromination of nicotinoyl chloride (VI-87) reported by Bachman and Micucci (*82*). This reaction is certainly surprising in view of the inertness of unsubstituted pyridine toward bromine. An earlier report (*83*) describes the preparation of a mixture of 4-bromo- and 5-bromonicotinic acids by pyrolysis of nicotinic acid perbromide. The 5-bromo isomer (VI-88) brominates further to give 4,5-dibromonicotinic acid, while 4-bromonicotinic acid does not react with additional bromine.



(VI-89)

(VI-87)

(After hydrolysis)
(87%, from the acid)

(VI-88)

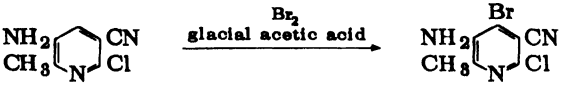
Aminopyridines are readily brominated under mild conditions. A good yield of 2-amino-3,5-dibromopyridine is obtained from 2-aminopyridine in aqueous solution (*84*). In an acid medium at room temperature both 2-amino-5-bromo- and 2-amino-3,5-dibromopyridines are formed (*85,86*). In ethanol with one mole of bromine, 2-amino-5-bromopyridine results (*72,87*). 6-Amino-2-picoline brominates in quite the same manner, giving 6-amino-5-bromo-2-picoline and then 6-amino-3,5-dibromo-2-picoline (*70*).

The gas phase bromination of 2-aminopyridine has been studied (*60,85*). At 500° the reaction is violent, with complex products and much carbonization. The reaction may be moderated by diluting the gas stream wth nitrogen, then giving about 25% yields of a mixture of which 55–75% consists of 2-amino-3-, -5-, and -6-bromopyridines.

Bis(2-pyridyl)amine is brominated in acetic acid to a yellow-orange dibromo derivative, m.p. 191°, hydrochloride, m.p. 253–254° (*88*).

Additional bromine may be easily introduced into the remaining open positions of monohaloaminopyridines. Bromine in acetic acid at room temperature transforms 2-amino-3-bromopyridine to the 3,5-dibromo derivative (*53*). Similarly 2-amino-4-bromopyridine gives first 2-amino-4,5-dibromopyridine and then 2-amino-3,4,5-tribromopyridine (*53,89*). 2-Amino-6-bromopyridine gives both 2-amino-3,5,6-tribromopyridine and 2-amino-5,6-dibromopyridine (*89*). 2-Amino-4,6-dibromopyridine gives 2-amino-4,5,6-tribromopyridine with limited bromine at 0°, and 2-amino-3,4,5,6-tetrabromopyridine with excess bromine at room temperature. Both 4-amino-2-bromopyridine and 4-amino-3-bromopyridine are easily brominated, and give 4-amino-2,3-dibromopyridine and 4-amino-3,5-dibromopyridine, respectively. 4-Amino-2,6-dibromopyridine gives rise to either 4-amino-2,3,6-tribromopyridine or 4-amino-2,3,5,6-tetrabromopyridine, depending upon the amount of bromine used and the temperature of reaction. Thus it may be noticed that in each case the first bromine enters at the 5 position (unless 3 and 5 are equivalent in the molecule as in the 4-aminopyridine case), and the second enters at the 3 position (*cf.* Chapter IX).

Even a nitro group on the nucleus is not sufficient to overcome the activation of the amino group, and 2-amino-5-nitropyridine and its 6-methyl analogue are brominated to give the corresponding 2-amino-3-bromo-5-nitropyridine and 6-amino-5-bromo-3-nitro-2-picoline (*90*). Bromine in glacial acetic acid gives 5-amino-4-bromo-2-chloro-6-methylnicotinonitrile (VI-91) in 80% yield from VI-90 (*91*).

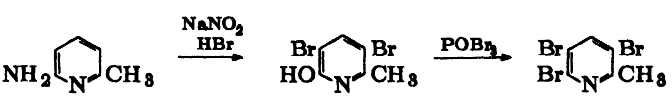


(VI-92)

(VI-90) (VI-91)

By contrast, 6-methyl-5-hydroxy-3-pyridinemethanol forms a molecular addition compound with bromine under these conditions.

Additional nuclear bromination sometimes occurs during the course of conversion of pyridinols to the corresponding bromopyridines. When 6-methyl-2-pyridinol is treated with a large excess of phosphorus pentabromide, 3,5.6-tribromo-2-picoline is formed in addition to the expected 6-bromo-2-picoline (*92*). VI-94 is also formed when 6-amino-2-picoline is treated with sodium nitrite in hydrobromic acid, followed by phosphorus oxybromide (VI-95). The formation of VI-93 under the conditions shown is rather surprising. In view of the difficulty encountered in oxidizing VI-94

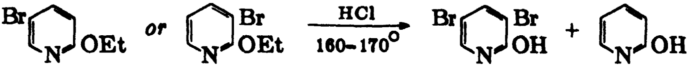


(VI-95)

(VI-93) (VI-94)

to the corresponding 3,5,6-tribromopicolinic acid for structure proof, there is some question of its structure.

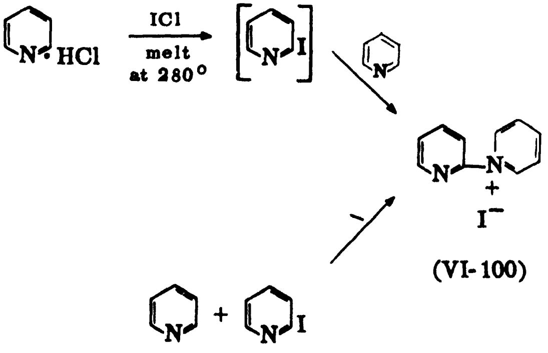
Bromine enters the pyridine nucleus via a disproportionation which takes place during the cleavage of 3-bromo-2-ethoxypyridine (VI-97) with hydrogen chloride. The 5-bromo analog (VI-96) undergoes a similar reaction (*29*). In the same manner 2,3,4-tribromopyridine is formed along with 2,4-dibromopyridine from 2,4-dimethoxypyridine and phosphorus pentabromide; and from 2,4-pyridinediol is obtained 2,3,4,5-tetrabromopyridine (*53*). 2,6-Pyridinediol with phosphorus pentabromide gives 2,3,6-tribromo- and 2,3,5,6-tetrabromopyridines (*93,94*).



(VI-99)

(VI-96) (VI-97) (VI-98)

(e) Iodination. The reaction of pyridine with iodine or iodine chloride in the gas phase gives low conversion to 3,5-diiodopyridine and pentaiodopyridine. Pyridine in oleum at 300–320° is iodinated by the addition of iodine to give 3-iodopyridine in 17–19% yield along with some 3,5-diiodopyridine (*95*). When 2-picoline is treated in a similar manner 5-iodo-2-picoline is formed (*96*). The iodination of pyridine hydrochloride by iodine chloride, or by iodine at 280°, is indicated by the isolation of 1-(2-pyridyl)pyridinium iodide (VI-100), the same product as formed from 2-iodopyridine



(VI-100)

(VI-101)

and pyridine (*97*). Small amounts of 2-iodopyridine, 3,5-diiodopyridine, and pentaiodopyridine are also said to be in the products from this reaction (*95*).

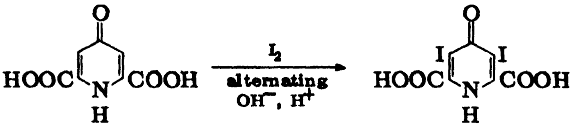
When 2,6-dibromopyridine is treated with hydriodic acid in a sealed tube a rather complex mixture results from which 3,5-diiodo-2-pyridinol may be isolated (*98*). A similar reaction is observed for 2-bromopyridine, giving rise to 3,5-diiodo-4-pyridinol.

3,5-Diiodo-2-pyridinol is formed in 85% yield from 2-pyridinol with iodine chloride in dilute hydrochloric acid (*102*). The same product may be obtained by the action of iodine with potassium carbonate on the salt of 2-pyridinol (*99*) or 5-iodo-2-pyridinol (*100*), or in small amounts from 2-pyridinol with iodine and hydrogen peroxide at 90–95° (*101*).

4-Pyridinol and iodine chloride in acid solution are reported by Dohrn and Diedrich (*32,103*) to give 3,5-diiodo-4-pyridinol. 2,6-Dimethyl-4-pyridinol and 2,6-dimethyl-4-pyridinethiol iodinate in exactly the same manner to give 3,5-diiodo-2,6-dimethyl-4-pyridinol and the corresponding thiol (*104*). 1-Methyl-2(1*H*)-pyridone reacts with iodine chloride in acetic acid to form 3,5-diiodo-1-methyl-2(1*H*)-pyridone (*105*).

3-Pyridinol reacts readily with iodine in mildly alkaline solution to give 2-iodo-3-pyridinol in 90% yield (*106*).

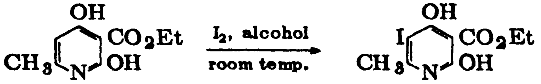
When 4-hydroxypicolinic acid is treated with iodine in a warm solution made alternately acidic and alkaline, two atoms of iodine are introduced, giving 3,5-diiodo-4-hydroxypicolinic acid. A similar procedure gives 3,5-diiodo-6-hydroxypicolinic acid (*32*). Displacement of the carboxyl group results, along with iodination, when 6-hydroxynicotinic acid is treated with iodine in the presence of iodide and carbonate (*107*). Under milder conditions, 6-hydroxy-2,5-diiodonicotinic acid results (*108*). Iodination of chelidamic acid by the alternating acid-alkali technique produces 3,5-diiodochelidamic acid (VI-102) (*32,109,110*). A quantitative yield of this acid is reported with iodine chloride in sodium bicarbonate solution (*104*). Improved iodination procedures have made *iodoxyl* (the disodium salt of 3,5-diiodo-1-methylchelidamic acid) and *diodone* (the sodium salt of 3,5-diiodo-4(1*H*)-pyridone-1-acetic acid), important x-ray con-



(VI-103)

(VI-102)

trast media, readily available (*109*). Iodine in alcohol reacts slowly with ethyl 2,4-dihydroxy-6-methylnicotinate at room temperature to give the 5-iodo derivative (VI-104) (*75*).



(VI-105)

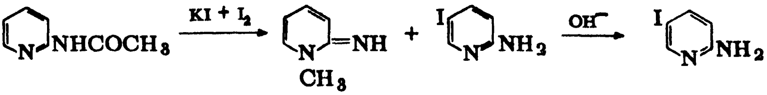
(VI-104)

6-Hydroxy-5-nitronicotinic acid is somewhat more difficult to iodinate than the unnitrated parent acid, and again the carboxyl group is displaced by iodine in the process (*107*).

Iodination and other halogenation reactions of pyridinols are also discussed in Chapter XII.

The alternating acid-alkali technique of Dohrn and Diedrich has been applied to the iodination of 2-aminopyridine (*99*). In this case only a single atom of iodine is introduced. The same aminoiodopyridine is formed when 2-aminopyridine is iodinated over pumice at 510°, and in good yield by electrolytic iodination of the amine in iodide solution in the presence of hydrogen iodide binding agents (*111*). A second atom of iodine is introduced by iodine chloride in tertiary butyl alcohol at 65° (*99*). This reagent gives first a molecular addition compound with 2-aminopyridine in dilute hydrochloric acid. Decomposition of this periodide leads to the 5-iodo derivative (*112*). A series of 2-alkylamino-5-iodopyridines and 2-amino-3-ethyl-5-iodo-6-methylpyridine have been prepared in this manner (*113*). Magidson and Menschikoff (*101*) have described similar iodination of 2-aminopyridine using hydrogen iodide with either hydrogen peroxide or potassium iodate, or better with iodine and potassium iodide.

2-Acetamidopyridine, treated similarly, forms a mixture of the hydroiodide of 1,2-dihydro-2-imino-1-methylpyridine (VI-106) and the periodide of 2-amino-5-iodopyridine.



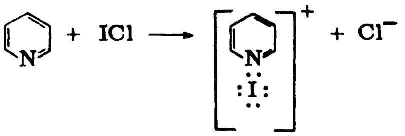
(VI-106) Periodide (VI-107) (VI-108)

These rather sluggish iodinations may be contrasted to the facile brominations and chlorinations previously discussed.

b. Halogen Molecular Addition Compounds

Pyridine and many substituted pyridines react with halogen in the cold to form molecular addition compounds. While such complexes may be formed in water in some cases, it has been shown (*114*) that in general an inert solvent, such as carbon tetrachloride, serves better.

The structure of these addition compounds has been the subject of considerable study. Williams (*114*) has shown that the halogen is rather firmly bound, since vapor pressure measurements indicate little if any free halogen in equilibrium with the addition compound. Due to the difficulty in finding a solvent of high dielectric constant in which the simple addition compounds could be dissolved, the dissociation was measured only in pyridine. The dissociation was found to be surprisingly small, and to vary with the concentration in a manner resembling pyridinium salts in the same solvent, thus suggesting a salt-like structure for the addition compounds. From these observations Williams postulated VI-109 as a



(VI-110)

(VI-109)

possible structure. The addition compounds react readily with acids to form salts, still retaining the complexed halogen.

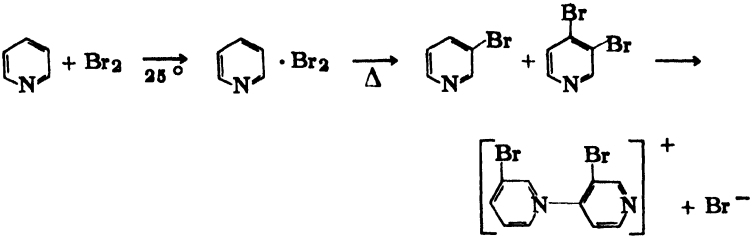
The halogen addition compounds are generally not stable toward heat. Decomposition at elevated temperatures may lead to substitution of the pyridine nucleus by halogen, and serves in some instances as the preparative method of choice for a halopyridine. The relative stability of several addition compounds has been estimated by Williams (*114*). In order of increasing stability in air (towards water vapor), or towards ethanol are $C_5H_5N \cdot F_2$, $C_5H_5N \cdot Cl_2$, $C_5H_5N \cdot Br_2$, $C_5H_5N \cdot BrCl$, $C_5H_5N \cdot BrI$, and $C_5H_5N \cdot ClI$. The addition compounds formed with iodine chloride are among the most stable.

(a) Fluorine Addition Compounds. Fluorine is said to form a molecular addition compound with pyridine at low temperature (*115*). This material decomposes at –40° to 0°. A similar complex, which is stable at room temperature, is formed by 2-fluoropyridine and fluorine, and is a potent fluorinating agent.

(b) Chlorine Addition Compounds. The passage of chlorine into an aqueous solution of pyridine produces nitrogen, carbonic acid, and dichloroacetic acid (*116*). Early investigation showed that an addition compound is formed in chloroform solution. More recently a crystalline compound, $C_5H_5N \cdot Cl_2$, m.p. 46°, has been isolated from equimolar amounts of chlorine and pyridine in carbon tetrachloride (*114*). This compound is rather unstable and fumes in air.

(c) Bromine Addition Compounds. Bromine water added to aqueous pyridine is said to give a precipitate of "pyridine bromide" (*117*). This product is more likely the hydrated perbromide salt, $C_5H_5N \cdot Br_2 \cdot HBr \cdot 2H_2O$, described more fully by Trowbridge and Diehl (*118*). Bromine in carbon tetrachloride added to pyridine gives a "dibromide" which is isolable at room temperature (*114*). Other pyridine-bromine adducts with varying amounts of bromine are noted in the earlier literature and are recorded in Table VI-1 (p. 371). An addition compound of pyridine and bromine may be formed directly by adding bromine to pyridine if the temperature is kept below 25° (*57*). Pyrolysis of this material without isolation gives rise to a mixture of about equal parts of polymer and volatile product. Upon fractionation of the latter, a main fraction which appears to consist of about equal parts of 3-bromo- and 3,4-dibromopyridines is obtained. These two substances soon react further to form a quaternary salt (VI-111).

(d) Iodine Addition Compounds. Solid complexes of pyridine with one-half, one, and two moles of iodine are mentioned in the early literature (*119,120*). Later workers report failure to isolate


(VI-111)

these, but note a marked color change, attributed (*114*) to the formation of a complex in solution, when pyridine is mixed with iodine in an inert solvent. The infrared absorption spectrum of a solution of iodine in pyridine is quite different from that of pyridine alone (*121*). As iodine itself in an inert solvent does not absorb in the infrared, this marked effect on the spectrum of pyridine suggests strong bonding forces between pyridine and iodine.

(e) Interhalogen Addition Compounds. Pyridine forms stable addition compounds with the halogen halides. With bromine chloride, iodine chloride, iodine bromide, and iodine trichloride, isolable compounds have been reported (*114,122*). Chlorine dioxide also forms a crystalline addition compound, which may be used as a convenient source of this gaseous reagent (*123*).

(f) Acid Salts of Addition Compounds. As already noted, the electronic structure of the pyridine-halogen addition compounds is such that they still can act as bases to form salts. The complexed halogen may, however, react with the acid anion. At any rate, when the preparation is carried out in acid solution, or when acid is added to the simple addition compounds, salts frequently are formed.

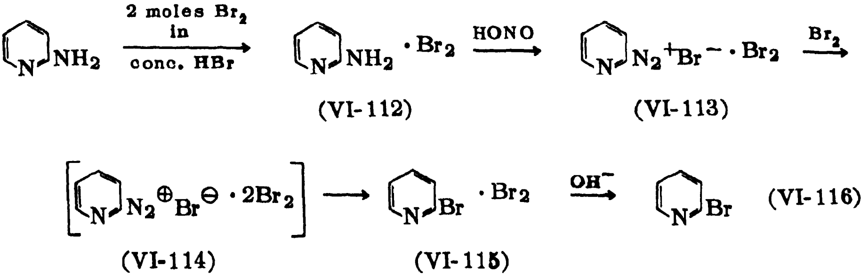
A solution of pyridine hydrochloride slowly absorbs chlorine to form a semi-solid perchloride which melts completely at about 90°. When this compound is heated rapidly to 160–180°, some chlorination occurs. From the product may be isolated 3-chloro- and 3,5-dichloropyridines, each in about 4% yield (57). In a similar manner molten pyridine hydrochloride readily reacts with bromine to form a perbromohydrohalide which, when heated to 160–170°, decomposes with smooth evolution of hydrogen chloride to form 3-bromopyridine (37%) and 3,5-dibromopyridine (27%) as principal products (57). By increasing the amount of bromine, the amount of dibromopyridine formed may be increased at the expense of the monobromo. While the hydrobromide works almost equally well in this useful synthetic procedure if heated to 250°, pyridine sulfate appears to form no perbromide, and a mixture of this salt with bromine merely loses the latter upon heating. Crystalline perbromohydrobromides are obtained when bromine is added to pyridine hydrobromide in glacial acetic acid (*124*). With one mole of bromine a compound containing 47% perbromide bromine, $C_5H_5N \cdot HBr \cdot Br_2$, m.p. 132–134°, is obtained; while with one-half mole of bromine a product of m.p. 101–103° and with but 39.7% perbromide bromine is formed. The latter may be decomposed thermally to form the 3-bromo- and 3,5-dibromopyridines as already described, but with no advantage in yield over the *in situ* process (*124*).

Pyridine hydrochloride forms a very stable addition compound with iodine. This product is converted to pentaiodopyridine upon heating (*57*).

Many other halogen addition compounds of the salts of pyridine are reported (see Table VI-2, p. 371). A complex perbromide hydrate results when bromine is added to pyridine in aqueous hydrobromic acid (*118*). This compound has found use as a mild brominating agent (*125*). The interhalogen addition complexes also form salts. Thus pyridine hydrochloride reacts with iodine chloride to form $C_5H_5N \cdot HCl \cdot ICl$ (*122,126*). The acid may be removed from this salt by treating it with base. The corresponding complex with iodine trichloride may be prepared by treating the iodine chloride complex with chlorine in an inert medium (*126*), or by direct interaction of pyridine and iodine trichloride (*122*). This complex also forms a salt.

(g) Addition Compounds of Substituted Pyridines. Bromine forms an addition compound, m.p. 95°, with 2-picoline (*57*). Unlike the bromine addition compounds of pyridine, this gives rise only to polymeric material on thermal decomposition. The hydrochloride of each of the three picolines is said to form a stable addition compound with bromine. Again in contrast with the pyridine compounds, these picoline complexes lose hydrogen chloride when heated, without substitution of the nucleus by bromine. Only 2-picoline hydrochloride perbromide gives any isolable bromopicoline upon thermal decomposition, 3–4% of an unidentified bromo-2-picoline (57).

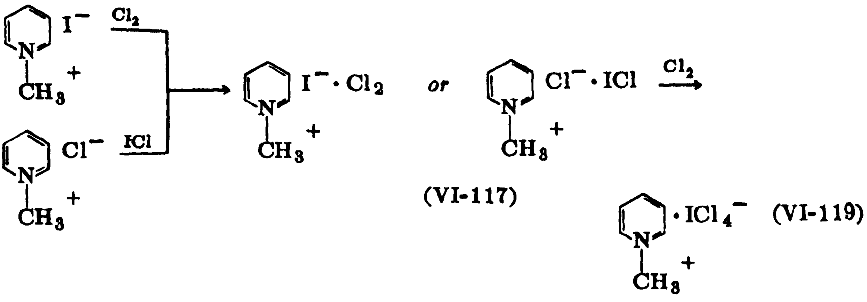
Aminopyridines very readily form addition compounds with halogen. Treatment of 2-aminopyridine with chlorine in alcohol gives 80% of a chlorine addition compound which, upon heating in petroleum ether, is converted to a mixture of mono- and dichloroaminopyridines (*34*). Craig (*127*) developed the following improved process for preparing 2-bromopyridine in 87% yield from 2-aminopyridine, based on the observation that neither 2-aminopyridine nor 2-bromopyridine is brominated by bromine in hydrobromic acid solution. Two moles of bromine are added to a solution of 2-aminopyridine in concentrated hydrobromic acid. A crystalline perbromide (VI-112) forms. Sodium nitrite is added to the cold suspension, and the amine is diazotized. The diazotate (VI-113) then adds a second mole of bromine to form VI-114. This unstable intermediate in turn decomposes to form VI-115 from which the desired 2-bromopyridine may be liberated by the addition of alkali.



(VI-112) (VI-113) (VI-114) (VI-115) (VI-116)

This procedure does not work for the preparation of 2-iodopyridine, perhaps because of the greater stability of the corresponding periodo intermediates (*127*). When 2-aminopyridine is treated with iodine in a solution of potassium iodide, a periodide of 2-amino-5-iodopyridine, m.p. 144–146°, results (*101*). Conversion of this intermediate to 2-amino-5-iodopyridine has already been described (p. 320). A perbromide of 6-amino-3-nitro-2-picoline, m.p. 230°, is formed along with the bromide in acetic acid (*36*). Nicotinic acid complexes with bromine when the two are mixed in chloroform (*83*). Thermal decomposition of this perbromide gives a mixture of 4-bromo- and 5-bromonicotinic acids.

Just as the acid salts of pyridine readily form addition compounds with halogen, so do the 1-alkylpyridinium salts. Examples of these compounds are listed in Table VI-3 (p. 371). In general this type of complex is prepared in the same manner and has properties quite like those already discussed. Thus 1-methylpyridinium iodide reacts with chlorine to form a perhalide (VI-117) (*116*). The same compound results when 1-methylpyridinium chloride (in hydrochloric acid) is treated with iodine chloride (*128*). Additional chlorine transforms VI-117 to VI-118.



(VI-117)

(VI-119)

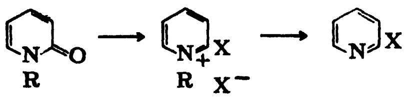
(VI-118)

The molecular addition compounds of substituted pyridines and their salts are listed in Table VI-4 (p. 372).

c. From Pyridinols, Pyridones, and Related Starting Materials

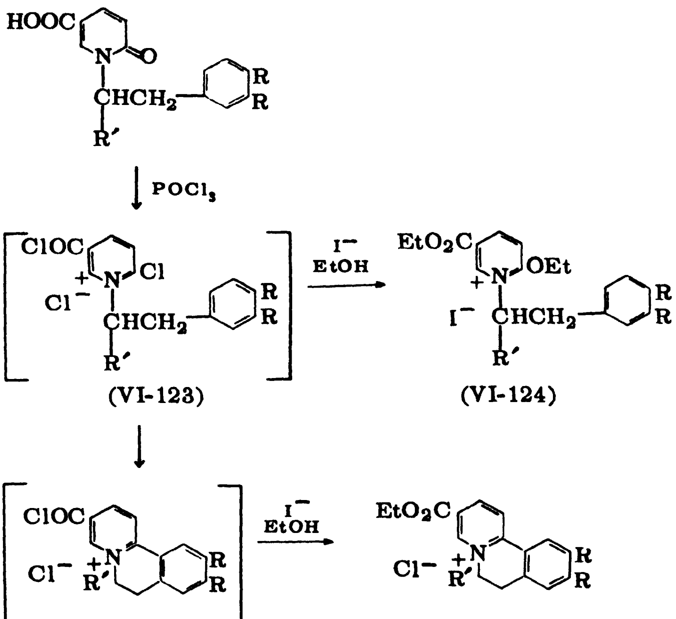
When 2- or 4-pyridinols are treated with halogenating agents such as the phosphorus halides, phosgene, or thionyl chloride, the corresponding halopyridines usually result. This method has been widely used to prepare 2- and 4-halopyridines. Hydroxyl at 3 (or 5) is not usually so replaced. 1-Alkyl-2- or 4-pyridones, 1-alkylthiopyridones and similar starting materials have also been used successfully (*cf.* Chapter XII).

A mechanism for the reaction, particularly for the transformation of 1-alkylpyridones, has been suggested by Wiley (*133*). The process is visualized as proceeding through a 2-halopyridinium salt (VI-122). Ordinarily the intermediate (VI-120) is not isolated, but gives the 2-halopyridine (VI-121) with the loss of the 1-alkyl group. Evidence for this route is found in the isolation of reaction products such as VI-124 and VI-126 which still retain the 1-substitution. In



(VI-120) (VI-121) (VI-122)

this example the over-all reaction from the β-phenylalkylpyridone to the final product serves as a new and useful route to N-bridgehead heterocyclics. The starting materials are prepared from methyl coumalate and a β-phenylethylamine. The phenethyl group is observed to remain intact in the related conversion of 5-ethyl-1-phenethyl-2(1*H*)-pyridone to 2-chloro-5-ethyl-1-phenethylpyridinium chloride (*166*). In this case, however, the reaction does not proceed further to undergo the Bischler-Napieralski cyclization.

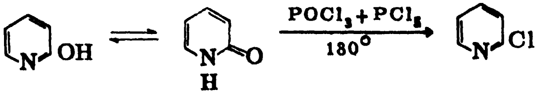


(VI-123) (VI-124) (VI-125) (VI-126) (VI-127)

	R	R′
(a)	$-OCH_3$	H
(b)	$-OCH_2O-$	H
(c)	H	H
(d)	H	$-CH_3$

(d gave no product corresponding to VI-126).

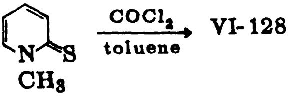
2-Chloropyridine (VI-128) was first prepared by v. Pechmann and Baltzer (*134*), who heated 2-pyridinol with phosphorus penta-



(VI-129)

(VI-128)

chloride and a little phosphorus oxychloride at 130°. Phosphorus trichloride at 150° converts 4-pyridinol to 4-chloropyridine (*135*), but this reaction is more easily accomplished with phosphorus pentachloride (*136*), or phosphorus oxychloride (*137*), or best, in 71% yield, with a mixture of the two reagents (*138*). The phosphorus pentachloride–phosphorus oxychloride combination has been used with 1-methyl-2(1*H*)-pyridone to prepare 2-chloropyridine in 80% yield (*41*), and in nearly quantitative yield by the refined procedure of Fargher and Furness (*139*). Methyl chloride is a by-product. The yield is also excellent when phosgene (usually used in toluene) or thionyl chloride is substituted for the phosphorus halides (*135,140*). The yield of 2-chloropyridine is but 50% when 1-methyl-2(1*H*)-pyridinethione reacts with phosgene in toluene (VI-130) (*140*).



(VI-130)

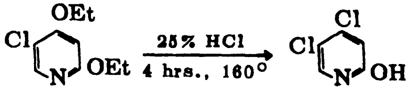
In a similar procedure 1-methyl-4(1*H*)-pyridone serves as a starting material for 4-chloropyridine (*141*). The scope of the reaction is indicated by the preparation of 2-chloropyridine from 1-(2-quinolyl)-2(1*H*)-pyridone with phosphorus oxychloride (*167*).

2-Bromopyridine has been prepared by heating 1-methyl-2(1*H*)-pyridone with a mixture of phosphorus pentabromide and phosphorus oxybromide at 150° (*41*). A little nuclear bromination gives 2,5-dibromopyridine as a by-product. 4-Bromopyridine has been prepared from 4-pyridinol with the same reagent mixture (*142*), again with a little nuclear bromination to form 2,4,6-tribromopyridine. Phosphorus pentabromide alone has also been used for this reaction (*138*).

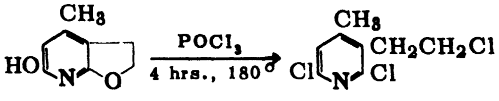
When a 2,4- or a 2,6-diol is used, two atoms of halogen may be introduced. Thus the best preparative method for 2,4-dibromopyridine is to treat 2,4-pyridinediol with phosphorus oxybromide (*53*). The relative unreactivity of the 3-hydroxyl is shown by the formation of 4-bromo-3-pyridinol when 3,4-pyridinediol is heated with phosphorus oxybromide (*67*). 3-Pyridinol is, however, converted to 3-chloropyridine by phosphorus pentachloride (*450*), or better by phenylphosphonic dichloride (*454*), a very useful reagent for hydroxyl replacement.

Polyhalopyridines are readily prepared from halopyridinols, halo-1-alkylpyridones, and halopyridinediols (Tables VI-5, VI-6, and VI-7, pp. 373 ff.).

Cleavage of an alkoxy side chain with replacement by halogen has already been noted (p. 313). A further example is the preparation of 4,5-dichloro-2-pyridinol (VI-132) from 5-chloro-2,4-diethoxypyridine (VI-131) by heating with a limited amount of 25% hydrochloric acid (*30*). Similarly, when 2,3-dihydro-4-methylfuro[2,3-b]pyridin-6-ol is treated with phosphorus oxychloride the ether ring is opened to form VI-135 (*143*). An unidentified dichloro compound is formed under milder conditions.

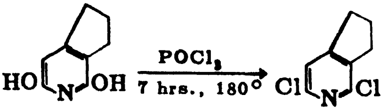


(VI-131) (VI-132) (VI-133)



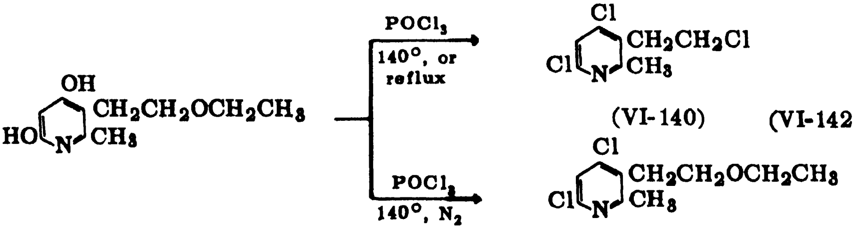
(VI-134) (VI-135) (VI-136)

The hydoxyl replacement method has been widely used to prepare halo derivatives of alkyl- and arylpyridines (Table VI-8). A typical example is the conversion of 6-ethyl-4-methyl-2-pyridinol to 2-chloro-6-ethyl-4-picoline (*144*). Prelog (*145,146*) has used similar conversions in the syntheses of pyridine derivatives which are related to degradation products from alkaloids, as in the conversion of 6,7-dihydro-5*H*-2-pyrindine-1,3-diol (VI-137) to 1,3-dichloro-6,7-dihydro-5*H*-2-pyrindine (VI-138). That arylpyridinols react similarly is shown in the preparation of 6-chloro-2-phenylpyridine from 6-phenyl-2-pyridinol (*147*). Phosphorus oxychloride transforms 3-phenyl-2,6-pyridinediol and its *p*-chloro derivative to the corresponding 3-aryl-2,6-dichloropyridine (*40*). Bromine is introduced similarly, as in the preparation of 6-bromo-3-picoline from 5-methyl-2-pyridinol (*87*), with phosphorus oxybromide the usual reagent. Other examples are listed in Table VI-8 (pp. 376 f.).



(VI-137) (VI-138) (VI-139)

Similar to the cleavage of nuclear alkoxyl which has already been described is the cleavage of side-chain ethers under the vigorous conditions of the reaction. Thus when 5-ethoxyethyl-6-methyl-2,4-pyridinediol is heated to 140° (*148*), or under reflux (*149*), with phosphorus oxychloride, 4,6-dichloro-3-(2-chloroethyl)-2-picoline (VI-140) results. When this same reaction is run under nitrogen at high pressure, however, the product is 4,6-dichloro-3-ethoxyethyl-2-picoline (VI-141).



(VI-140) (VI-141) (VI-142)

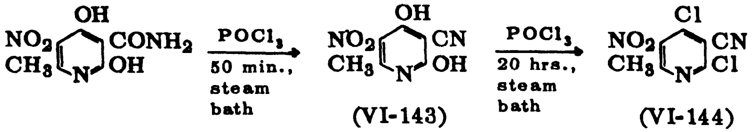
Nitropyridinols have been used frequently as precursors of halonitropyridines. The latter compounds are valuable intermediates in the preparation of aminopyridines by reduction, with either removal or retention of the halogen. By diazotization of aminohalopyridines it is possible to prepare a variety of polyhalopyridines, often with mixed halogen.

The easily obtained 5-nitro-2-pyridinol may be transformed to either 2-chloro-5-nitropyridine or 2-bromo-5-nitropyridine by treatment with suitable halogenating agents (*151,152*). 1-Methyl-5-nitro-2(1*H*)-pyridone works equally well as a starting material, and with this, phosgene in toluene is said to be the reagent of choice (*154*). The 1-ethyl and 1-benzyl derivatives have also been employed with phosphorus pentachloride and phosphorus oxychloride (*140,153*). Other halonitropyridines so prepared are listed in Table VI-9 (p. 378).

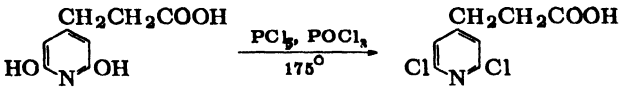
In some cases a nuclear amino group does not interfere. Thus 6-amino-5-phenyl-2-pyridinol has been transformed to 2-amino-6-chloro-3-phenylpyridine (*40*). Similarly 4-amino-2-chloro-6,7-dihydro-5*H*-1-pyrindine has been prepared from 4-amino-6,7-dihydro-5*H*-1-pyrindin-2-ol with phosphorus pentachloride (*69*). The conversion of 4-aminopyridine 1-oxide to 4-benzoylamino-2-chloropyridine by benzoyl chloride is analogous (*171*).

A number of halopyridinecarboxylic acids have been prepared by this method. 6-Hydroxynicotinic acid is smoothly converted by phosphorus pentachloride or phosphorus oxychloride to the acid chloride, 6-chloronicotinoyl chloride, which upon hydrolysis gives 6-chloronicotinic acid (*99,161,162*). (Other examples noted give similarly the acid chloride before water treatment, but are discussed in terms of the acid.) A mixture of phosphorus pentachloride and phosphorus oxychloride readily converts 6-ethyl-2-hydroxyisonicotinic acid to 2-chloro-6-ethylisonicotinic acid (*163*). 2,4-Dihydroxynicotinic acid is transformed to 2,4-dibromonicotinic acid when warmed with phosphorus oxybromide (*53*). Halogen may already be present. A mixture of phosphorus oxychloride and phosphorus pentachloride, or the latter alone, converts 3,5-dichloro-, 3,5-dibromo-, or 3,5-diiodo-4-hydroxypicolinic acid and 3,5-diiodochelidamic acid to the expected 4-chloro derivatives (*33*). Hydroxynitriles also may be employed. Thus 2-hydroxy-4,6-dimethylnicotinonitrile is converted to 2-chloro-4,6-dimethylnicotinonitrile by phosphorus oxychloride (*164*). Acetoxyl survives the reaction also, as illustrated in the conversion of 5-acetoxy-2-hydroxy-4,6-dimethylnicotinonitrile to 5-acetoxy-2-chloro-4,6-dimethylnicotinonitrile (*165*). Similar reactions give the 2-chloro-5,6-dimethyl, 2-chloro-6-methyl (*172*), 2-chloro-5-nitro (*91*), 4,6-dichloro (*173*), 2-chloro-4,6-bis(methoxymethyl) (*174*), and 2-chloro-4-ethoxymethyl-6-methyl-5-nitro (*175*) derivatives of nicotinonitrile.

The nitrile group sometimes undergoes hydrolysis. In the preparation of 2,6-dichloroisonicotinonitrile from the 2,6-diol, 2,6-dichloroisonicotinic acid is also formed (*176*). By contrast 2,6-dihydroxyisonicotinamide, 4-ethoxymethyl-2-hydroxy-6-methylnicotinamide (*179*), and 2,4-dihydroxy-6-methylnicotinamide (*177*) are transformed to the corresponding halonitriles by phosphorus halides. 2,6-Dihydroxyisonicotinic acid gives the 2,6-dihalo acid with the same reagents (*178*). Dehydration of the amide appears to proceed before replacement of hydroxyl, as shown by the conversion of 2,4-dihydroxy-6-methyl-5-nitronicotinamide first to VI-143 and then to VI-144 (*177*). Thionyl chloride, on the other hand, replaces the hydroxyl groups but leaves the amide group intact. The carboxylic acid group need not be attached directly to the ring, as illustrated in the preparation of VI-146 from the 2,6-dihydroxy precursor (*180*).

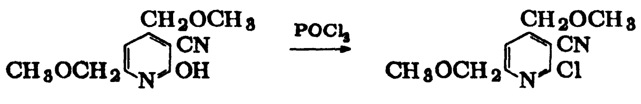


(VI-143) (VI-144) (VI-145)



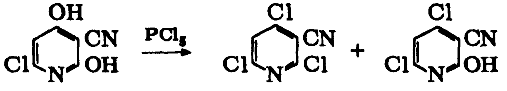
(VI-146) (VI-147)

The same conditions fail, however, to give the 3-cyano derivative of VI-146 from the corresponding diol. In direct contrast is the conversion of 2-hydroxy-4,6-bis(methoxymethyl)nicotinonitrile to the 2-chloro derivative (VI-148), illustrating also that side-chain ethers need not necessarily be cleaved (*174*). Schroeter and Finck (*181*) report difficulty in effecting complete replacement of the 2-hydroxyl



(VI-148) (VI-149)

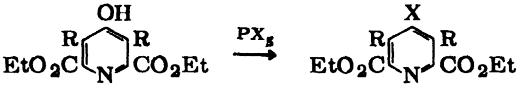
of 6-chloronorricinine (VI-150), and obtain a mixture of (VI-151) and VI-152. Better results are obtained with the disodium salt of VI-150 (*182*), which gives a good yield of 2,4,6-trichloronicotinonitrile (VI-151) with phosphorus pentachloride.



(VI-153)

(VI-150) (VI-151) (VI-152)

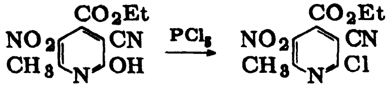
The ester function withstands the reaction conditions. Ethyl 6-hydroxy-2-methylnicotinate is transformed by phosphorus oxychloride to ethyl 6-chloro-2-methylnicotinate (*79*). Similarly ethyl 2-chloro-3-cyano-6-methyl-5-nitroisonicotinate is formed from ethyl 3-cyano-2-hydroxy-6-methyl-5-nitroisonicotinate by heating with phosphorus oxychloride in chlorobenzene (*183*). Halogen is introduced into halochelidamic esters by phosphorus pentahalides (VI-154). Hydroxy-ester-nitriles may also be used as starting materials.



(VI-154)

	R	X
(a)	Cl	Cl
(b)	I	Cl
(c)	I	Br
(d)	Br	Br

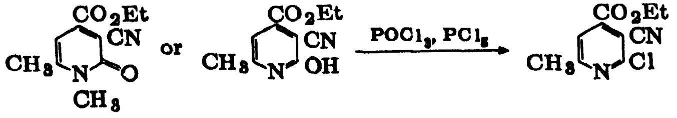
Thus phosphorus pentachloride converts VI-155 to the chloro derivative (VI-156) in a sequence of reactions leading to pyridoxine



(VI-157)

(VI-155) (VI-156)

(*183*). The related pyridones (VI-158 or VI-159) react in a similar manner (*185*). 6-Bromo- and 6-chloro-5-nitronicotinic acids have been made from 6-hydroxy-5-nitronicotinic acid with phosphorus halides (*159*). Failure to obtain the expected 6-chloro-5-nitronico-



(VI-158) (VI-159) (VI-160) (VI-161)

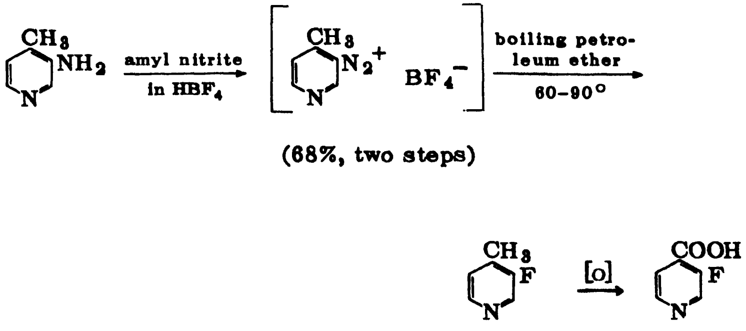
tinic acid from 1-methyl-5-carboxy-3-nitro-2(1*H*)-pyridone upon heating with phosphorus chlorides is noted by Berrie and co-workers (*159*).

Related starting materials have not been studied extensively. Wibaut and Broekman (*138*) have noted the formation of 1-(4-pyridyl)-4(1*H*)-pyridone (or perhaps 1-(4-pyridyl)-4-hydroxypyridinium chloride) when sodium 4-pyridinesulfonate is heated with phosphorus pentachloride. They suggest that the reaction proceeds through a displacement of the sulfonic acid group to form 4-chloropyridine as an intermediate in a manner similar to that observed with 4-pyridinols. 4-Chloropyridine itself was isolated by King and Ware (*186*), who used 4-pyridinesulfonic acid as a starting material. The action of chlorine on 4-pyridinethiol also leads to a small amount of 4-chloropyridine. The barium salt of 3,5-pyridinedisulfonic acid is transformed by phosphorus pentachloride at 200° to 3,5-dichloropyridine, along with some 2,3,5-trichloropyridine (*187*).

d. From Aminopyridines

Aminopyridines have been used as starting materials for the preparation of a wide variety of halopyridines (*cf.* Chapter IX). 3-Aminopyridines may be diazotized in the same manner as aniline, and halogen then introduced by the usual Sandmeyer, Gattermann, or Schiemann techniques. For 2- and 4-aminopyridines a somewhat different procedure is necessary. To introduce bromine at position 2 it has been found advantageous first to prepare the perbromo hydrobromide, and then to treat this substance with nitrite (*127*). This method has come to be known as the Craig procedure. In many other cases it has been found possible to obtain the 2- or 4-halopyridine by merely adding nitrite to a solution of the aminopyridine in hydrohalic acid, usually followed by warming. Yields are often quite good.

2-Fluoropyridine was first prepared by treating 2-aminopyridine with amyl nitrite in hydrofluoric acid (*203*). This method of preparation has been studied in detail by subsequent workers (*204–206*). Despite a report that 2-aminopyridine is not converted to a diazonium fluosilicate (*207*), the best reported yield (42%) is obtained by treating it in 30% aqueous fluosilicic acid with sodium nitrite, followed by warming to 40–50° for an hour (*204*). The preparation of 2-fluoro-5-nitropyridine has been accomplished by treating 2-amino-5-nitropyridine in 60% hydrofluoric acid at 0° with sodium nitrite (*208*). Similarly, 4-fluoropyridine has been obtained from 4-aminopyridine (*451*). Diazotization of a solution of 3-aminopyridine in fluoboric acid followed by warming gives a 50% yield of 3-fluoropyridine (*205*). Other conditions are decidedly inferior; for example, the Gattermann method gives a yield of 27% (*209*), while addition of ethyl nitrite to a solution of the amine in aqueous fluosilicic acid gives a 36% yield (*204*). Difficulty due to the insolubility of the intermediate diazonium fluoborate is encountered in the conversion of 5-aminonicotinic acid (or its esters) to 5-fluoronicotinic acid by the Schiemann reaction (ethyl nitrite in fluoboric acid) (*168*). A poor yield can be obtained from the ester in fluosilicic acid. A 60% yield of 5-fluoro-3-picoline is obtained by the Schiemann procedure (*168*), suggesting that a better route to the fluoro acid would be by oxidation of the fluoropicoline. Just such a sequence has been employed to prepare 3-fluoroisonicotinic acid (VI-163), which was desired for conversion to the hydrazide (*210*).



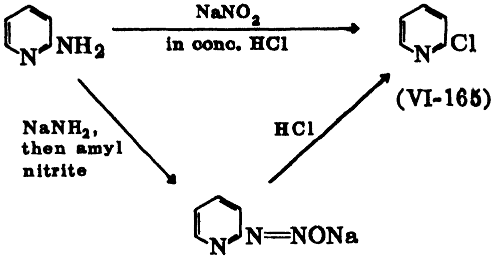
(68%, two steps)

(VI-164)

(VI-162) (VI-163)

2-Chloropyridine (VI-165) results when 2-aminopyridine is treated with sodium nitrite in concentrated hydrochloric acid (*203*).

The reaction presumably proceeds through the diazotate. An alternative procedure is to treat the sodium salt (VI-166) with acid. 4-



(VI-166)

(VI-167)

Chloropyridine may be prepared from 4-aminopyridine by the same procedure, with yields reported to range from quantitative (*211*) down to 50%. Diazotization of 4-nitraminopyridine in hydrochloric acid leads to 4-chloropyridine in good yield. If, however, the mixture is heated in a sealed tube to 100°, a dichloropyridine is formed (*212*). To prepare 3-chloropyridine from 3-aminopyridine the Gattermann or Sandmeyer procedures must be used, and yields of 65% and 34%, respectively, are obtained (*209*).

In the Craig procedure (*127,214*) 2-aminopyridine is first converted to the hydrobromide of the bromine molecular addition compound, which by treatment with sodium nitrite in the cold is transformed into the hydrobromide of 2-bromopyridine. About 3% of 2-pyridinol is said to be formed also (*215*). When the temperature is allowed to rise above 10° during the nitrite treatment, some 2,5-dibromopyridine is formed too (*216*). Treatment of 2-aminopyridine in hydrobromic acid with sodium nitrite directly gives but a low yield of 2-bromopyridine (*203,224*). A somewhat better yield can be had by adding copper during the conversion, but nothing to match the Craig procedure is obtained. 2-Bromopyridine may also be prepared by treating the sodium salt (VI-166) in hydrobromic acid with amyl nitrite (*20*). 4-Bromopyridine is readily prepared by treating 4-nitraminopyridine, a nitration product of 4-aminopyridine, with sodium nitrite in hydrobromic acid (*142*). For the preparation of 3-bromopyridine from 3-aminopyridine, the

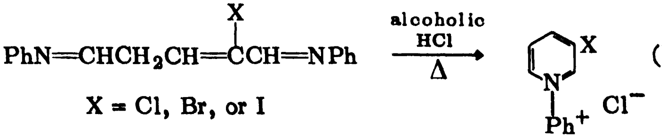
Gattermann procedure is again superior to the Sandmeyer, with yields of 56% and 30%, respectively (*203,209*).

To convert 2-aminopyridine to 2-iodopyridine, diazotization is performed in hydriodic acid solution (*203,224*). Iodide may be introduced as the potassium salt, permitting the use of dilute hydrochloric acid as a solvent. Both 3-iodo- and 4-iodopyridines have been prepared in this manner (*209,218,219*).

Substituted halopyridines prepared from the corresponding aminopyridines by diazotization are listed in Table VI-10 (pp. 379 ff.). The widely varied substituent groups include halogen, carbonyl, alkoxy, carboxy, carboalkoxy, nitro, hydroxy, cyano, alkyl, and aryl.

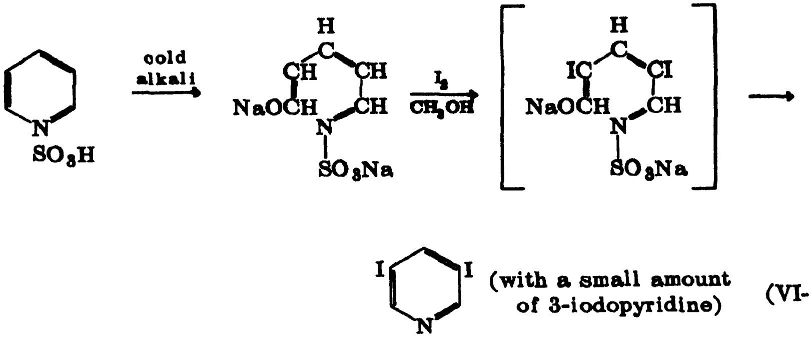
e. Other Methods

(a) Involving Ring Closure. Several halopyridines have been prepared by cyclization of open-chain compounds. In some of these halogen attached to the starting material appears in the resulting pyridine, while in other cases halogen is introduced during the course of the cyclization. An early example is the synthesis of 3-chloropyridine from α-chloroglutaconic dialdehyde and ammonia by Hantzsch (*241*). In similar reactions Baumgarten (*242*) has obtained 3-bromopyridine and 3-iodopyridine from the corresponding α-haloglutaconic dialdehydes. If the dianilide of the dialdehyde is heated with alcoholic hydrochloric acid, a 3-halo-1-phenylpyridinium chloride results (VI-168) (*242,243*). Glutarimide is converted by



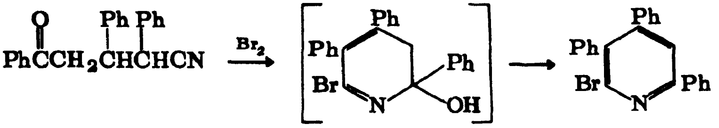
(VI-168)

phosphorus pentachloride to a mixture of mono-, di-, and trichloroaminopyridines (*11*). 2,5,6-Trichloro-3-picoline and 2,6-dichloro-3,5-lutidine are formed from α-methylglutarimide and α,α′-dimethylglutarimide by the same reagent (*94*). A related reaction is the transformation of 1-pyridiniumsulfonic acid to 3,5-diiodopyridine



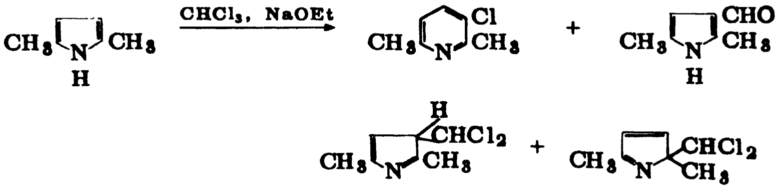
(VI-169)

(VI-169) (*244*). 1,4-Dihydro-3-hydroxy-4-oxopicolinic acid forms from 3-hydroxy-4-oxo-4*H*-pyran-6-carboxylic (comenic) acid with ammonia, and is converted by phosphorus oxychloride to a mixture of penta- and hexachloropicolines (*45*). δ-Oxo-α,β,δ-triphenylvaleronitrile is oxidatively cyclized by bromine to give 2-bromo-3,4,6-triphenylpyridine in good yield (VI-170) (*217*). Ethyl β-aminocrotonate is converted by phosphorus oxychloride to ethyl 4-chloro-2,6-dimethylnicotinate in 42% yield (*245*). A somewhat similar reaction has been used to prepare 5-chloro-2-hydroxy-4,6-dimethylnicotinonitrile from cyanoacetamide and 3-chloro-2,4-pentanedione (*165*). Ethyl 2-bromo-4,6-diphenylnicotinate is the product in two steps (base catalyzed condensation, and bromine oxidation in hot acetic acid) from benzalacetophenone and ethyl cyanoacetate (*246*).



(VI-170)

(b) Ring Enlargement Reactions. One of the earliest recorded syntheses of 3-halopyridines is the treatment of pyrrylpotassium with a haloform to give a small amount of 3-chloro- or 3-bromopyridine (*61,247*). Alternatively, pyrrole may be refluxed with a mixture of bromoform and sodium or potassium alkoxide to obtain 3-bromopyridine (*48*). In studying the reaction under a variety of conditions to improve the yield, Alexander *et al.* (*248*) noted the difficulty in using pyrrylpotassium, but were unable to obtain a good yield with the alkoxide technique or with pyrryllithium. Extension of the reaction to benzal chloride or methylene iodide was largely unsuccessful, although a little 3-phenylpyridine was so prepared. Rice and Londergan (*249*) have reported that a better yield may be had by passing pyrrole and chloroform through a hot tube (550°), but find that a little 2-chloropyridine is formed also. The reaction has been extended to the preparation of 3-bromo-2,6-lutidine from 2,5-dimethylpyrrole with bromoform and sodium ethoxide (*250*). Chloroform, on the other hand, gave a mixture of products, as did 2,4-dimethylpyrrole and bromoform under the same conditions (VI-171)



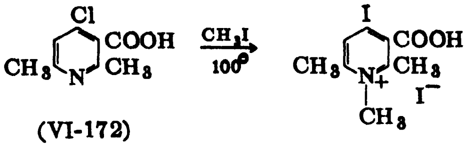
(VI-171)

(*251*). Ring enlargement reactions for the synthesis of pyridine derivatives are discussed extensively in Chapter II (pp. 153 ff. and 226 ff.).

(c) **Halogen Exchange.** It has been observed that halogen in the 2 or 4 position on the pyridine nucleus may be displaced by another halogen. While this reaction has not been studied sufficiently to demonstrate its scope, it has found some use as a preparative method. For example, 3-amino-2-bromo-5-chloropyridine gives 3-amino-2,5-dichloropyridine when refluxed in hydrochloric acid (*159*). Similarly, 3-amino-5-bromo-2-chloropyridine is formed from 3-amino-2,5-dibromopyridine. Thionyl chloride has been used to obtain 4,5-dichloropicolinic acid from 5-chloro-4-iodopicolinic acid (*38*). Den Hertog and de Bruyn (*29*) have reported a series of displacements with 25% hydrochloric acid at 160°. Thus 6-bromo-2-ethoxypyridine is converted to 6-chloro-2-pyridinol (along with some 2,6-pyridinediol); 2-bromo-3-ethoxypyridine is changed into 2-chloro-3-pyridinol (with some 2,3-pyridinediol); 6-bromo-3,5-dichloro-2-ethoxypyridine is transformed to 3,5,6-trichloro-2-pyridinol; and 2,5,6-tribromo-3-ethoxypyridine to 5-bromo-2,6-dichloro-3-pyridinol. Side reactions other than ether hydrolysis may occur; thus 3,5-dibromo-2-pyridinol and 2-pyridinol are formed from either 5-bromo-2-ethoxypyridine or 3-bromo-2-ethoxypyridine under these same conditions. Rearrangement occurs to give 5-bromo-2,4-pyridinediol when 3-bromo-2,4-pyridinediol is heated with hydrobromic acid (*220*). When hydrochloric acid is used, however, the bromine of 3-bromo-2,4-pyridinediol is displaced without rearrangement, to give 3-chloro-2,4-pyridinediol (*220*).

The method has been used to prepare several iodopyridines. Baker *et al.* (*252*) report that boiling 2-bromopyridine for six hours with strong hydriodic acid is the method of choice for preparing 2-iodopyridine. When 4-chloropyridine is heated for eighteen hours with hydriodic acid (*d* 1.8) at 195°, 4-iodopyridine is formed (*135*). In the same manner 3,4,5-triiodo-2,6-lutidine is formed from 4-chloro-3,5-diiodo-2,6-lutidine (*104*). 4-Iodopicolinic acid may be prepared from 4-chloropicolinic acid by refluxing with hydriodic acid and red phosphorus (*37*). If this reaction mixture is heated to 180°, dehalogenation occurs, and picolinic acid is the main product (*37,231*). 5-Chloro-4-iodopicolinic acid and 5-chloropicolinic acid are formed when methyl 4,5,6-trichloropicolinate is heated with hydriodic acid and red phosphorus (*38*). Hydriodic acid converts 4-chloro-3,5-diiodo-2,6-pyridinedicarboxylic acid to 3,4,5-triiodo-2,6-pyridinedicarboxylic acid in 83% yield (*104*). Klingsberg (*253*) has found that the displacement takes place smoothly in neutral solvents. Thus 6-iodonicotinic acid may be had in quantitative yield from 6-chloronicotinic acid by refluxing with sodium iodide in methyl ethyl ketone (reaction proceeds much more slowly in the lower-boiling acetone). Baker *et al.* (*252*) report that this procedure is not satisfactory for converting 2-bromopyridine to 2-iodopyridine. Boiling hydriodic acid converts 2,6-dichloroisonicotinic acid (*254*) and 2,4-dichloro-6-methylnicotinonitrile (*177*) to the corresponding diiodo compounds. Under these conditions 2,4-dichloro-6-methyl-5-nitronicotinonitrile undergoes not only displacement of the chlorine, but also reduction of the nitro group to give 5-amino-2,4-diiodo-6-methylnicotinonitrile. When this mixture of reactants is digested at a temperature somewhat below the boiling point, the nitro group remains intact. A carboxyl group is removed when 4-chloro-2,6-pyridinedicarboxylic acid is heated with hydriodic acid and red phosphorus, giving 4-iodopicolinic acid (*33*). Graf (*38*) has noted selective displacement of 6- over 4-chlorine in 2-amino-4,6-dichloropyridine: refluxing hydriodic acid gives 2-amino-4-chloro-6-iodopyridine. The chlorine of 4-chloro-2,6-dimethylnicotinic acid (VI-

172) is displaced during the preparation of the methiodide under rather mild conditions (*245*).

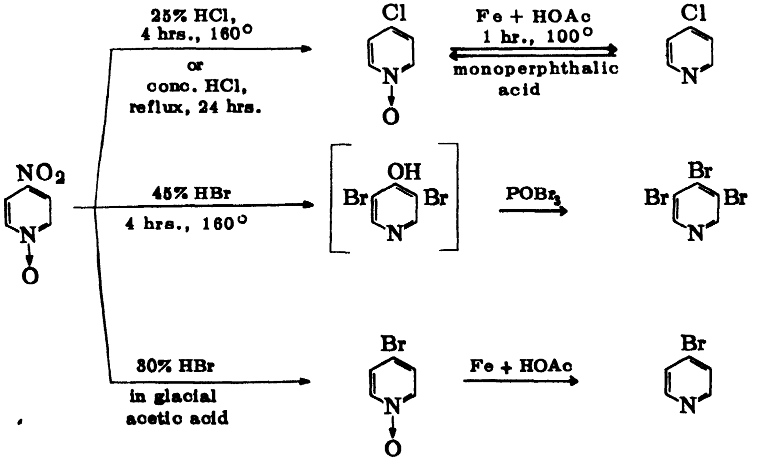


(VI-172)

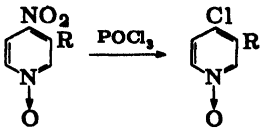
(VI-173)

Several fluoronitropyridines have been prepared from the corresponding chloro compounds by the action of potassium fluoride in dimethylformamide (*453*).

Related to the displacement of one halogen by another is the displacement of other groups from the nucleus by halogen. 2-Chloro-6-methyl-3-pyridinol may be prepared from 6-methyl-2-nitro-3-pyridinol by heating with hydrochloric acid (*36*). 2-Bromo-3-ethoxy-6-nitropyridine is converted by 40% hydrobromic acid (four hours at 130°) to 2,6-dibromo-3-pyridinol (*67*). Hydrogen bromide in glacial acetic acid transforms 3,5-diethoxy-2,6-dinitropyridine to 2-bromo-3,5-diethoxy-6-nitropyridine upon short treatment, and further to 2,6-dibromo-3,5-diethoxypyridine when heated more vigorously (*74*). Ethyl 2-hydroxy-4,6-diphenylnicotinate gives ethyl 2-bromo-4,6-diphenylnicotinate on treating with bromine (*246*), and 5-nitro-2-pyridinethiol gives 2-chloro-5-nitropyridine when treated with chlorine (*9*). Similar displacements in the 1-oxide series have found considerable preparative use (VI-174, VI-175, VI-176) (*21,255–257*).

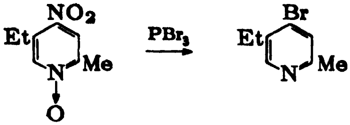


(VI-174)



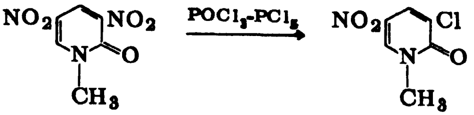
(VI-175)

R = H or Br



(VI-176)

The 3-nitro group of 1-methyl-3,5-dinitro-2(1*H*)-pyridone is displaced by chlorine upon heating with phosphorus oxychloride and phosphorus pentachloride (VI-177) (*159*). Deep-seated rearrange-



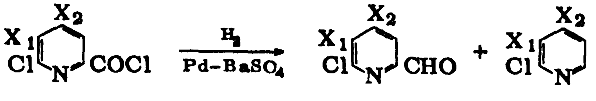
(VI-177)

ment evidently occurs when 2-bromo- or 2,6-dibromopyridine is treated with hydriodic acid in a sealed tube, and 3,5-diiodo-4-pyridinol or 3,5-diiodo-2-pyridinol is isolated (*98*).

(d) Displacement of the Halomercuri Group. Pyridine is readily mercurated in the 3 position, and the resulting mercury compounds serve as starting materials for halopyridines. Thus 3-bromopyridine has been prepared by treating 3-chloromercuripyridine with bromine and sodium bromide (*50*). These same reagents convert 3-iodomercuripyridine to 3-bromopyridine (*258*) and 3,5-bis(iodomercuri)pyridine to 3,5-dibromopyridine. A similar reaction occurs with 4-chloromercuripyridine 1-oxide, giving 4-bromopyridine 1-oxide (*259*).

(e) Removal of Other Functional Groups. Halopyridinecarboxylic acids lose carbon dioxide at elevated temperatures to give halopyridines. In this manner 2,3-dichloropyridine has been prepared from 5,6-dichloronicotinic acid upon distillation under reduced pressure at 150°, and 3,5-dichloropyridine from 3,5-dichloroisonicotinic acid after twenty hours at 230° (*37*), or from 3,5-dichloropicolinic acid upon distillation from glycerine (*6*). 5-Iodopicolinic acid gives 3-iodopyridine at temperatures above 210° (*96*). As a preparative reaction, distillation of the silver salt of the acid is sometimes advantageous. Thus destructive distillation of silver 2,6-dichloroisonicotinate (*254*) and silver 2,6-dibromoisonicotinate (*176*) gives the 2,6-dihalopyridine.

Decarboxylation occurs as a side reaction during the Rosenmund reduction of chloropicolinoyl chlorides to the corresponding aldehydes (VI-178) (*260,261*). Similar results are observed for 2,6-dichloro- and 2,6-dibromoisonicotinoyl chlorides (*176,262*). Decarboxylation has been observed in the bromination of pyridinecarboxylic acids. Thus quinolinic acid, upon treatment with bromine at 120–130°, gives 2,5-dibromopyridine (*263*). Under these same conditions, pyridinepentacarboxylic acid gives the same product. In a like manner 3,5-dibromo-2,6-lutidine is obtained from 2,6-lutidine-3,5-dicarboxylic acid, and 3,5-dibromo-2,4,6-collidine from 2,4,6-collidine-3,5-dicarboxylic acid, both brominated as the potassium salt. A sulfonic acid group is removed in a similar manner when 3-pyridinesulfonic acid is treated with bromine in boiling aqueous solution, and a very small yield of a compound first thought to be a dibromopyridine, m.p. 164–165°, is the product (*264*). This material is said by den Hertog and Wibaut (*59*), however, to be 4-amino-3,5-dibromopyridine, and evidently arises through a 1-(3,5-dibromo-4-pyridyl)pyridinium salt, in a manner much as suggested earlier by Sell and Dootson (*10*).



(VI-178)

(a) $X_1 = X_2 = Cl$
(b) $X_1 = H, X_2 = Cl$
(c) $X_1 = Cl, X_2 = H$

Halogen exchange and halogen removal are reported by Graf (*38*), who obtained 5-chloro-, 4,5-dichloro-, and 5-chloro-4-iodopicolinic acids from 4,5,6-trichloropicolinic acid with hydriodic acid and red phosphorus.

Diazotization of 3-amino-2,6-diiodopyridine in alcohol gives 2,6-diiodopyridine along with some 3-ethoxy-2,6-diiodopyridine (*97*). 2-Hydrazino-3-iodopyridine is oxidized by copper sulfate to 3-iodopyridine in 50% yield (*266*).

The stability of the pyridine nucleus permits a fused benzene ring to be oxidized to give the corresponding quinolinic acid. In this manner 4-chloroquinolinic acid has been prepared from 4-chloroquinoline (*267*), as has 4,5,6-trichloroquinolinic acid from 2,3,4-trichloroquinoline (*160*), and 5-bromoquinolinic acid from 3-bromoquinoline (*39*). Potassium permanganate in neutral solution is the usual oxidizing agent; it has also been used to oxidize 3,5,6-tribromo-2-picoline to 3,5,6-tribromopicolinic acid (*92*), and 5-iodo-2-picoline to 5-iodopicolinic acid (*96*).

2. Properties

The halopyridines range from liquids with low freezing point to high melting solids. The odor, when described, is usually said to be rather more pleasant than that of pyridine itself.

The base strengths of the 2-halopyridines have been measured (*274*). From these it was possible to estimate the relative polar effects of the halogens (values applicable to halo compounds in general) free from other effects such as F-strain, sterically inhibited resonance, and hydrogen bonding. Base strength increases regularly from 2-fluoropyridine, a very weak base, to 3-iodopyridine as shown in Table VI-11 (p. 384). The surprisingly great influence of fluorine at position 2 is said to indicate a much greater importance of inductive effect than resonance effect. When the fluorine is at 3, the inductive effect becomes much smaller, and resonance effects become much more important. These base strengths have been correlated with absorption spectra, which tend to support the same conclusions. Spectral studies of solutions of 2- and 3-fluoropyridines show that the fluorine atom produces a bathochromic shift in the pyridine maximum. The spectrum is dependent upon the solvent. 2-Fluoropyridine does not form a salt with hydrogen chloride (10% in ethanol) while 2-fluoroquinoline does so (*276*). The interaction of chlorine with the ring of 2-chloropyridine has been ascertained by measuring the electric moment. The observed values agree in magnitude with those for other similarly substituted heterocyclics and chlorobenzenes (*277*).

Properties of the known halopyridines are listed in Tables VI-12 to VI-15 (pp. 385 ff.).

3. Reactions

a. Introduction

Nuclear halopyridines undergo a wide variety of reactions. Among these, aminolysis and reduction have been most widely studied. Halogen at the 2 or 4 position is of course more reactive, in general, than at the 3 position. Young and Amstutz (*284*) have noted that the chlorine of 2-chloropyridine is replaced less readily than the 2-halogen of either quinoline or pyrimidine, and conclude that this shows a greater electron density about the 2 carbon atom of pyridine. Such an observation is in accord with Coulson's qualitative theoretical values of electron density calculated by methods of molecular orbitals.

As indicated later in the more detailed discussion, the presence of other functional groups (or additional halogen) on the nucleus may greatly alter the reactivity of the halogen. Of particular interest is activation by a meta-directing group placed ortho or para to the halogen, particularly the influence of a 3-(or 5-)nitro group on halogen in the 2 or 4 position.

The relative reactivity of halogen is best studied in a series of monohalopyridines (a given halogen at position 2, 3, or 4) to avoid the complicating influence of the halogens on each other in the polyhalopyridines. Either 2- or 4-chloropyridine slowly reacts with itself at room temperature to form such salts as 4-chloro-1-(4-pyridyl)-pyridinium chloride (from 4-chloropyridine) or polycondensation products (*138*). 3-Chloropyridine and 3-bromopyridine are stable towards self-condensation, even at elevated temperatures. 2-Bromopyridine rather readily gives 2-bromo-1-(2-pyridyl)pyridinium bromide, and considerable caution must be taken to prevent 4-bromopyridine from decomposing in this manner. Cislak (*14*) says, however, that the instability of 4-halopyridines has been exaggerated. He notes particularly that these substances are stable in acid solution, and cites confirmatory evidence (*21,285*).

Neglecting interhalogen influences, the greater reactivity of 2- and 4-halogens as compared to 3- may be seen in selective reactions. Thus 3,4-dibromopyridine or 3-bromo-4-chloropyridine reacts with ammonia water when heated to give exclusively 4-amino-3-bromopyridine (*19,53*). Similarly 2,3,4,5-tetrabromopyridine gives 4-amino-2,3,5-tribromopyridine when warmed with alcoholic ammonia (*10*). 2-Chloro-3,5-diiodopyridine is converted to 2-amino-3,5-diiodopyridine by ammonia at 150° (*99*). One halogen of 2,6-dibromopyridine may be replaced selectively by ammonia to give 2-amino-6-bromopyridine (*54*). More vigorous treatment causes replacement of the other halogen. When 2,4-dichloropyridine is treated with ammonia for five hours at 170–180° a mixture containing 60% 4-amino-2-chloropyridine and 20% 2-amino-4-chloropyridine is obtained (*26*), again suggesting greater reactivity for halogen at 4. Conflicting evidence is available too, however. Thus 2,4,6-tribromopyridine is said to give 2,6-diamino-4-bromopyridine with either aqueous or anhydrous ammonia (*286*).

Similar evidence of relative reactivity is provided by the reduction of polyhalopyridines. 2,3,6-Tribromopyridine gives 2,3-dibromopyridine upon hydrogenation over palladium, while 2,4,6-tribromopyridine gives mainly 2,6-dibromopyridine under the same conditions (*53*). Halogen at 3 may be reduced under similar conditions, however, as shown in the reduction of 2,5,6-trichloro-3-cyclopentylpyridine to 3-cyclopentylpyridine with hydrogen over palladium-charcoal (*271*).

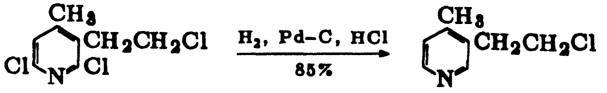
Unlike 3-halogen, 2- and 4-halogens are hydrolyzed readily. Thus hydrochloric acid at 350° converts 2-chloropyridine to 2-pyridinol, and 2,5-dichloropyridine to 5-chloro-2-pyridinol (*287*). 2,3-Dichloro-5-nitropyridine under the same conditions is transformed to 3-chloro-5-nitro-2-pyridinol, with the conversion of 2-chloro-5-nitropyridine to 5-nitro-2-pyridinol completing the series. The chlorine of 4-chloro-3-nitropyridine is rather more loosely bound, and hydrolyzes in warm water (*44*).

Alcoholysis proceeds more readily with 2- or 4-halogen of polyhalopyridines, as shown by the conversion of 2,3-dibromopyridine to 3-bromo-2-methoxypyridine with alcoholic sodium hydroxide (*29*), and of 2-chloro-5-iodopyridine to 5-iodo-2-methoxypyridine with sodium methodixe (*101*). 3-Bromopyridine does react with sodium alkoxide under vigorous conditions, and one or both of the halogens of 3,5-dibromopyridine are replaced by ethoxide at elevated temperature (*288,289*). These latter transformations are noteworthy in view of the failure of bromobenzene to react under similar conditions.

Displacement of halogen by cyano follows a reverse order. Thus while 3-bromopyridine may be converted smoothly to nicotinonitrile by cuprous cyanide (*257*), Brode and Bremer (*290*) fail to confirm the similar transformation for 2-bromopyridine as described by Craig (*127*). A poor yield of a mixture of picolinamide and picolinic acid is obtained when 2-bromopyridine is treated for an extended time with aqueous potassium cyanide and cuprous cyanide at 175°.

b. Hydrogenolysis, Reduction, and Coupling

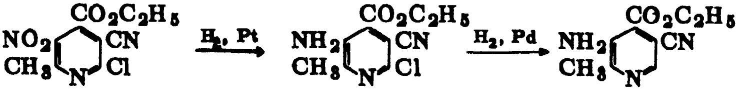
Halogen at 2 or 4 is readily removed by hydrogenolysis. In this manner a great variety of substituted pyridinols have been converted to the corresponding substituted pyridine via the sequence: 2-(or 4-)pyridinol to 2-(or 4-)halopyridine to pyridine. Typical of such reductive removal of halogen is the conversion of 6-bromo-2,4-dimethoxypyridine to 2,4-dimethoxypyridine by hydrogenation over palladium. The scope of this method is broad, and in general is limited only by the stability of other groups towards reduction. Comparative unreactivity of side-chain halogen is shown in the reduction of VI-179 to VI-180 (*143*). Platinum black and Raney nickel



(VI-181)

(VI-179) (VI-180)

are also employed as catalysts for such reductions. The greatest selectivity is shown by platinum black, which is usually employed to reduce a nitro group of a halonitropyridine and leave the halogen intact. Thus VI-182 is reduced first to the 6-chloro derivative (VI-183) over platinum and further to ethyl 3-amino-5-cyano-2-methyl-



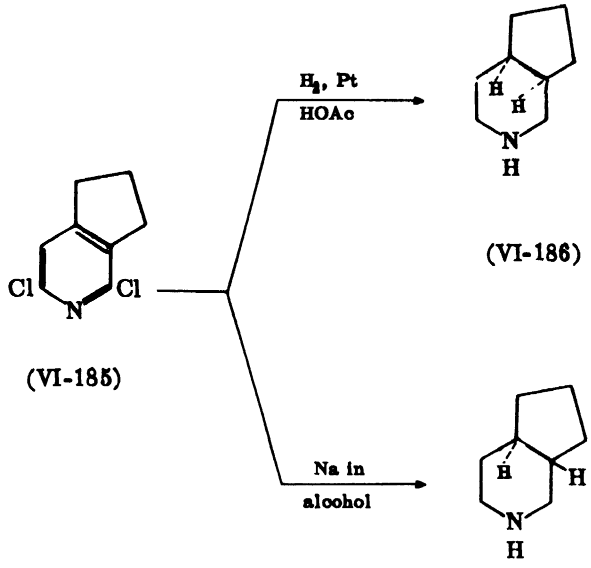
(VI-184)

(VI-182) (VI-183)

isonicotinate over palladium (*183*). Complete removal of halogen is usually achieved with Raney nickel.

Several chemical methods are also employed. Hydrogen iodide with red phosphorus removes halogen selectively. Thus 3,4,5-trichloro- and 3,4,5,6-tetrachloropicolinic acids are reduced to 3,5-dichloropicolinic acid by this reagent, and 3,5-dibromopicolinic acid is formed similarly from 3,5-dibromo-4-chloropicolinic acid (*33*). The same reaction with 3,5-diiodo-4-chloropicolinic acid gives a mixture of mono- and diiodopicolinic acids. Further evidence of the selectivity of this method is seen in the preparation of 2-chloro-3-ethyl-4-picoline from the 2,6-dichloro analogue (*201*). Zinc in acid removes 2- and 4-halogen, as in the reduction of 6-chloro-2,3,4-trimethylpyridine to 2,3,4-trimethylpyridine (*270*), and the conversion of 6-chloronorricinine to norricinine (*182*). Similarly, 4,6-dichloro-2-hydroxynicotinonitrile is reduced to 2-hydroxynicotinonitrile by zinc in dilute sulfuric acid (*181*). Stannous chloride, on the other hand, may be used to reduce a nitro group without removal of halogen. Thus while 6-chloro-5-nitro-2-picoline is reduced to 5-amino-2-picoline by hydrogen over palladium, stannous chloride in acid solution gives a good yield of 5-amino-6-chloro-2-picoline (*36*). A mixture of the two products is obtained by hydrogenation over platinum. An excellent yield of 3-amino-5-bromo-6-chloro-2-picoline and of 3-amino-6-chloro-2-picoline may be had by reduction of the corresponding nitro compounds with stannous chloride. Both of these haloaminopyridines may be further reduced to 3-amino-2-picoline by hydrogenation over palladium. Sodium in alcohol not only removes the halogen, but reduces the pyridine ring of 1,3-dichloro-5,6-dihydro-5*H*-2-pyrindine (VI-185) to form the *trans* perhydro compound (VI-187), while the *cis* perhydro compound (VI-186) results upon catalytic reduction in acid solution over platinum (*145*).

Halopyridines may undergo reductive coupling when heated with copper. Thus 2-bromo-4-picoline gives 4,4′-dimethyl-2,2′-bipyridine in 33% yield (*87*). 2-Bromo-3-picoline reacts in a similar manner. Halogen at 3 is inert under these conditions, and 2,5-dibromopyridine and 2-bromo-5-chloropyridine give the corresponding 5,5′-di-



(VI-185)

(VI-186)

(VI-187)

(VI-188)

halo-2,2′-bipyridines, albeit in rather poor yield. For 2-iodo-5-nitropyridine the coupling is best carried out in *p*-cymene to give 5,5′-dinitro-2,2′-bipyridine.

An alternative method for coupling halopyridines is to treat with sodium sulfide. 2-Chloro-5-nitropyridine is converted to 5,5′-dinitro-2,2′-bipyridine by this reagent (*291*).

c. Hydrolysis

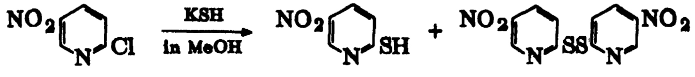
Halogen at either 2 or 4 readily undergoes hydrolysis, while at 3 it is quite stable toward either acid or alkaline hydrolysis. Hydrolysis apparently proceeds more readily under alkaline conditions. 2,6-Dibromopyridine is converted to 2,6-pyridinediol by aqueous alcoholic sodium hydroxide at 90°, while 70% sulfuric acid at 160° for six hours removes only one atom of bromine to give 6-bromo-2-pyridinol (*293*). 2-Chloropyridine is hydrolyzed to 2-pyridinol by aqueous potassium hydroxide (*292*). Aqueous sodium acetate or hydrochloric acid may be used to hydrolyze 4-chloro-2,6-lutidine, the former giving 4-acetoxy-2,6-lutidine (*104*).

Halogen at the 3 position is stable to normal hydrolytic conditions, but reacts in the presence of copper salts. Thus a mediocre yield of 3-pyridinol is obtained when 3-bromopyridine is treated with aqueous sodium hydroxide in the presence of cupric sulfate at 200° (*51*).

Hydrolysis of several substituted halopyridines is recorded. Potassium hydroxide in water converts 2-chloro-5-nitropyridine to 5-nitro-2-pyridinol (*292*). Concentrated hydrochloric acid in glacial acetic acid effects the conversion of 2-bromo-3-nitropyridine to 3-nitro-2-pyridinol (*159*). The same reagent converts 2-bromo-5-chloro-3-nitropyridine to 5-chloro-3-nitro-2-pyridinol, and 2,5-dibromo-3-nitropyridine to 5-bromo-3-nitro-2-pyridinol, again demonstrating the relative stability of halogen at position 3. Aqueous hydrochloric acid or 20% alkali hydrolyzes both the halogen and the cyano group of 6-chloronicotinonitrile. The 6-chloro acid results, however, when concentrated hydrochloric acid in ether is used (*294*). Both halogens remain intact in the preparation of 5,6-dichloronicotinic acid by the same procedure. Aqueous sodium hydroxide hydrolyzes only the 2-chlorine of 2,4,6-trichloronicotinonitrile, giving the 2-hydroxy derivative (*181*). Strong potassium hydroxide at 150° causes not only hydrolysis of the halogen of 6-chloro-2,4-dihydroxynicotinonitrile, but also loss of the cyano group (*36*). Hydroxyricinic acid may be prepared, however, by treating 6-chloro-3-cyano-4-hydroxy-1-methyl-2(1*H*)-pyridone with sodium hydroxide. 2,6-Dibromo-1-methylpyridinium iodide loses but one atom of bromine when treated with aqueous alkali at room temperature, to give 6-bromo-1-methyl-2(1*H*)-pyridone (*188*).

The preparation of pyridinols and pyridones from halopyridines is also discussed in Chapter XII.

With alkali hydrosulfide in alcohol, the halogen is displaced by a mercapto group. Thus 2-chloropyridine gives 2-pyridinethiol (and some 2-ethylmercaptopyridine) when treated with potassium hydrosulfide in ethanol (*295*). 2-Chloro-3-nitropyridine reacts similarly in methanol, but gives 2,2′-dithiobis(3-nitropyridine) as a by-product (VI-189) (*30,291*). In propylene glycol as solvent, 3-bromopyridine gives 3-pyridinethiol (*296*).



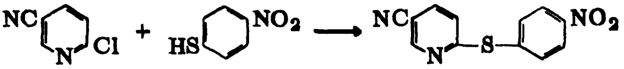
(VI-189)

d. Alcoholysis

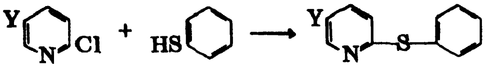
The halopyridines react with alkoxides to give the corresponding alkoxypyridines. As already noted, the ease of displacement decreases in the order 4 > 2 > 3. The conversion of 2,4-dichloropyridine to 2,4-dimethoxypyridine by sodium methoxide is typical (*20*). 2,4,6-Tribromopyridine gives 2,4,6-trimethoxypyridine if heated with sodium methoxide in methanol at 120° for two hours, but gives 2-bromo-4,6-dimethoxypyridine when refluxed for a like period, and 2,6-dibromo-4-methoxypyridine upon short boiling (*71*). The chlorine of 4-chloro-3-nitropyridine is readily replaced upon warming with methoxide in alcohol (*297*). By contrast, 2-chloro-3-nitropyridine and 2-chloro-5-nitropyridine are unaffected by boiling ethanol, while chloride is said to be slowly liberated at 30° by a 0.1 *M* solution of 4-chloro-3-nitropyridine in ethanol (*155*). The chlorine of 4-chloro-3,5-diiodopyridine is displaced by ethoxide (*298*), and 5-amino-2,4-dichloro- (or 4-bromo-) 6-methylnicotinonitrile is converted to the 4-methoxy derivative (*91*). The alcoholysis reaction has also been extended to the halopyridine 1-oxides, as shown by the conversion of 4-bromo-3-picoline 1-oxide to the corresponding 4-benzyloxy, 4-ethoxy, or 4-methoxy derivatives by treatment with the alkoxide in the corresponding alcohol (*25*). Normal displacement is also given by sodium phenoxide. Differences in the order of halogen reactivity are noted with variations in solvent. Thus 2,4,6-tribromopyridine gives 2,4,6-triphenoxypyridine with sodium phenoxide in phenol (36 hours, 195°). After 24 hours a mixture of 2,4-dibromo-6-phenoxy- and 4-bromo-2,6-diphenoxypyridine is obtained. Sodium phenoxide in water, on the other hand, leads to a mixture of the two latter halophenoxypyridines with starting material and 2,6-dibromo-4-phenoxypyridine, and when the latter compound is treated with phenoxide in phenol (24 hours, 195°) 2-bromo-4,6-diphenoxypyridine is the product (*299*).

The conversion of halogen compounds to ethers is further discussed in Chapter XII.

Halogen may be displaced similarly by alkyl, benzyl, or aryl thiols (VI-190) (*301*), (VI-191) (*300,302,303*), (the thiophenol may be



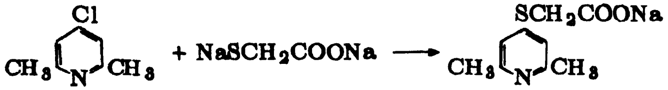
(VI-190)



(VI-191)

(Y = NO_2 or NH_2)

substituted) (*304*). 6-Chloronicotinonitrile is converted to the 6-amylmercapto derivative by amyl mercaptan (*301*). 4-Chloro-3,5-diiodopyridine reacts with thiosalicylic acid in the presence of sodium ethoxide in ethanol to give the expected 4-(*o*-carboxyphenylthio)-3,5-diiodopyridine (*298*). 4-Chloro-2,6-lutidine reacts with disodium thioacetate (VI-192) (*104*), and methyl 2-chloronicotinate and 3,5-di-



(VI-192)

bromo-2-chloropyridine react similarly (the latter giving sodium (3,5-dibromo-2-pyridylthio)acetate) (*238*).

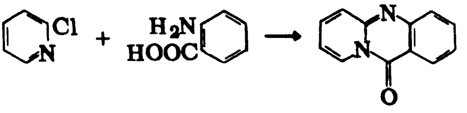
The preparation of sulfides and other sulfur compounds is further discussed in Chapter XV.

e. Aminolysis

Under a variety of conditions ammonia replaces halogen to give the corresponding aminopyridine. Thus merely heating 2-bromopyridine with ammonium hydroxide at 200° gives a 57% yield of 2-aminopyridine (*54*). Zinc chloride is said to facilitate the reaction of 2-chloropyridine with anhydrous ammonia (*41*). 2,6-Dichloropyridine is converted to 2-amino-6-chloropyridine by ammonium hydroxide in the presence of copper sulfate, while the same conditions fail with 3,5-dichloropyridine (*5*). This latter observation is a little surprising in view of the reported catalysis by copper salts in the ammonolysis of 3,5-dibromopyridine to 3,5-diaminopyridine (*51*), and several other cases of 3-halogen displacement

(*95–97,288,305*). Primary and secondary aliphatic amines react similarly with 2- and 4-halogens. A typical reaction is that of 4-chloropyridine with 1-(3-aminopropyl)piperidine to give 1-[3-(4-pyridylamino)propyl]piperidine (*306*). 2-Bromopyridine reacts with an excess of trimethylenediamine to give 2-(3-aminopropylamino)-pyridine, while an equimolar amount of this amine gives the symmetrical dipyridyldiamine (*216,307*). 2,6-Dihalopyridines are said to give 2-amino-6-(1-piperidyl)pyridine when treated sequentially with piperidine and ammonia (but either may be allowed to react first) (*308*). Halopyridine 1-oxides react similarly, as shown by the reaction of 4-chloro-3-picoline 1-oxide with morpholine to give 4-(4-morpholinyl)-3-picoline 1-oxide (*25*).

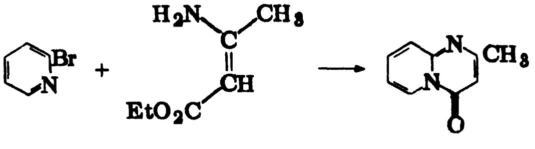
Halopyridines also react with aromatic amines. Thus 4-chloropyridine and aniline give 4-anilinopyridine (*309*). 2-Bromopyridine reacts similarly (*310*). 3-Halopyridines also react with aromatic amines, particularly when catalyzed by copper salts or copper bronze. Accordingly, 3-bromopyridine reacts with *o*-phenylenediamine to give 3-(*o*-aminoanilino)pyridine (*311*), and with anthranilic acid to give *N*-(3-pyridyl)anthranilic acid (*309*). The reaction of 2-chloropyridine with anthranilic acid leads to 11-pyrido[2,1-b]quinazolin-11-one (VI-193) (*312,313*), not to pyracridone as postulated by Räth



(VI-194)

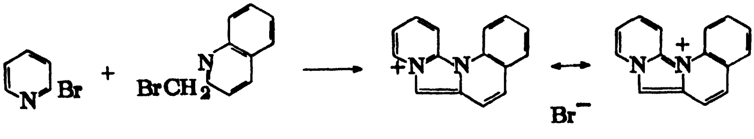
(VI-193)

(*315*). Anthranilic acid with 4-chloropyridine gives *N*-(4-pyridyl)-anthranilic acid, which fails to cyclize (*309*), while 2-chloro-5-nitropyridine reacts exactly like 2-chloropyridine. The ring nitrogen is involved when 2-bromopyridine reacts with ethyl *β*-aminocrotonate, and 2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one is formed (VI-195)



(VI-195)

(*316,317*). This same product was obtained by Palazzo and Tamburini (*269*) from 2-aminopyridine and aceotacetic ester, but was incorrectly formulated by these authors. *N*-Alkylation leads to cyclization through the pyridine nitrogen when 2-bromopyridine reacts with 2-bromomethylquinoline, giving the dehydro-7-pyrido[1,2-a]-quin[1,2-e]imidazolinium bromide (VI-196) (*318*).



(VI-196)

Secondary aromatic amines react with more difficulty, and require forcing conditions. The reaction of 2-bromopyridine with diphenylamine, which gives an 8% yield of 2-(diphenylamino)pyridine after nine hours of refluxing with potassium carbonate, potassium iodide, and copper bronze, is typical (*319*).

The reaction of 2-iodopyridine with 2-aminopyridine, carried out in boiling mesitylene with alkali, potassium iodide, and copper powder, leads to tris(2-pyridyl)amine (*88,320*). Bis(2-pyridyl)amine, which reacts readily with 2-iodopyridine, is not found in the reaction mixture. 2-Bromopyridine gives similar reactions with 2-aminopyridine. The sodium salt of bis(2-pyridyl)amine fails to react with 2-chloropyridine, and the sodium salt of 2-aminopyridine with 2-chloropyridine gives bis(2-pyridyl)amine, suggesting that the reaction is with the active hydrogen rather than with the anion. The sodium salt of 2-aminopyrimidine reacts with 2-bromopyridine at 150–160° to form 2-pyridyl-2′-pyrimidylamine, while neither this sodium salt nor that from 2-aminopyridine will react when refluxed with 2-bromopyridine in benzene.

2-Bromopyridine reacts with sulfanilamide in the presence of base (*i.e.*, with the potassium salt of the amide) to form sulfapyridine (*321*). In neutral solution, however, 2-chloropyridine reacts with the anilino nitrogen to give N^4-2-pyridylsulfanilamide (*151*). 2-Chloro-5-nitropyridine reacts with sulfanilamide to give a mixture of the two types of product even in the presence of base. A similar reaction occurs between 2-chloro-5-nitropyridine and *o*- or *p*-arsanilic acid to give the corresponding *N*-(5-nitro-2-pyridyl) derivative (*322*).

The aminolysis of halopyridines is also discussed in Chapter IX.

4-Chloropyridine reacts smoothly with hydrazine (hydrate) to form 4-hydrazinopyridine (*323*). 2-Hydrazinopyridine is more conveniently prepared from 2-bromopyridine than from 2-chloropyridine (*139,324,325*). 2,4,6-Trichloronicotinonitrile and hydrazine react to form 6-chloro-4-hydrazino-2-hydroxynicotinonitrile (*181*). 6-Chloro-3-nitro-2-picoline, 2-chloro-5-nitropyridine, and 6-chloro-5-nitro-2-picoline each reacts readily with hydrazine to give the corresponding hydrazinonitropyridine, thus indicating the general scope of this reaction (*157,326*). 4-Chloropyridine 1-oxide and 4-chloro-3-picoline 1-oxide react similarly with hydrazine (*25*). (*Cf.* p. 488.)

2-Chloropyridine reacts with hydrazoic acid to form pyridotetrazole (*327*), identical with that obtained by treating 2-hydrazinopyridine with nitrous acid (*139*). The reaction with hydrazoic acid has been extended to 2-chloro-3-(and 5-)nitropyridine (*216*).

f. Displacement by Cyano and Similar Groups

The ease of displacement of halogen at 3 as compared with that at 2 and 4 by the cyano group has already been discussed (p. 374). Halogen at 2 and 4 *may* be replaced, however, and such reactions are valuable as routes to substituted picolinic and isonicotinic acids. Among the halopyridines which have been successfully converted to the corresponding nitriles by reaction with cuprous cyanide are 4-bromo-2-ethyl-, 2-bromo-4-propyl-, 2-bromo-4-phenyl-, 2-bromo-6-phenyl-, and 2-bromo-3-nitropyridines. 2-Bromo-4-picoline and 4-bromo-5-ethyl-2-picoline react similarly (*159,227,230,255*). The latter reaction is of particular value since difficulty has been noted (*213*) in the preparation of 5-ethyl-2-methylisonicotinonitrile by a Sandmeyer reaction with the 4-amino compound. 4-Chloro-3,5-dinitropyridine reacts with cuprous cyanide in nitrobenzene to give 3,5-dinitroisonicotinonitrile, but the same reaction fails with the 2-methyl analogue (*146*).

Potassium thiocyanate displaces active nuclear halogen. 2-Chloro-3- and -5-nitropyridines have been converted to the corresponding thiocyanates in this manner (*328*).

When 5-bromo- or 5-iodo-2-pyridinol is treated with arsenic trioxide, potassium hydroxide, and copper sulfate in water, 2-hydroxy-

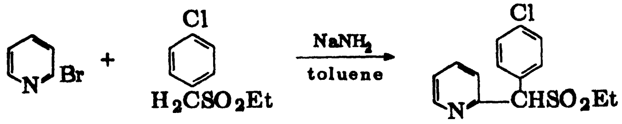
5-pyridinearsonic acid is produced (*329*). A similar reaction with 2-chloro-5-iodopyridine is said to give 2-chloro-5-pyridinearsonic acid, although no structure proof was offered.

g. C-Alkylation Reactions

Halogen of 2-, 4-, and 3-halopyridines may be displaced by anionic alkylating agents. 2-Bromopyridine pyridylates sodio diethyl ethylmalonate (*331*) and sodio ethyl α-methylbutyrate normally (*332*), but does not condense with malonic ester in the absence of alkali (*333*). 2-Chloro-5-nitro- (*334,335*), 4-chloro-3-nitro- (*297*), and 4-chloro-2,6-dicarbethoxypyridines (*336*) react with sodiomalonic ester in a similar fashion. Sodium hydroxide is used to catalyze the reaction of 2-chloropyridine with phenylacetonitrile to produce α-phenyl-2-pyridineacetonitrile (*337*), and sodium hydride with acetonitrile to produce bis(2-pyridyl)acetonitrile (*66*). 3-Bromopyridine reacts with phenylacetonitrile in exactly the same manner, indicating a somewhat greater activation of the 3 position by the inductive effect of the ring nitrogen than generally supposed (*338*). The pyridylation of nitriles is further discussed in Chapter XI; note especially Table XI-22.

2-Bromopyridine reacts with phenyllithium, giving 5% of 2-phenylpyridine (*272*), while the bromine of 2-bromo-3-picoline is displaced by *n*-butyl when it is treated with *n*-butylmagnesium bromide (*193*). By contrast, however, methylmagnesium iodide preferentially attacks the cyano group of 6-chloronicotinonitrile and forms 6-chloro-3-pyridyl methyl ketone (*339*).

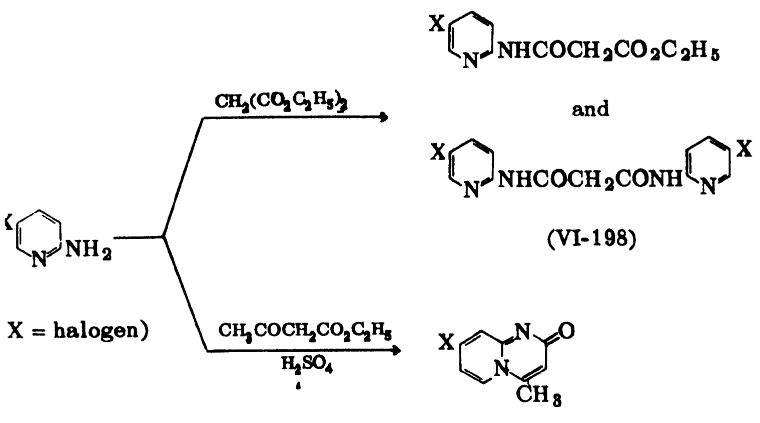
2-Bromopyridine reacts with alkyl benzyl sulfones in the presence of sodium amide to form alkyl phenyl(2-pyridyl)methyl sulfones (VI-197). 6-Bromo-2-picoline and 2-bromo-4-picoline have



(VI-197)

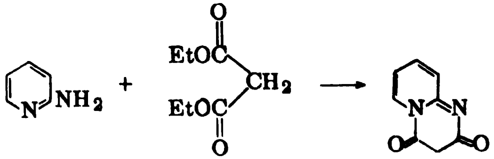
been used successfully in this reaction, and the phenyl group of the sulfone may be substituted (*e.g.*, with chlorine) (*340*). In a similar pyridylation, 2-bromopyridine reacts with 5-*n*-propyl- or 5-*n*-butyl-barbituric acid in dimethylaniline to give the 5-(2-pyridyl) derivative (*341*).

With malonic ester and no catalyst, 2-amino-5-halopyridines acylate at the amino nitrogen (VI-200) (*342*). (Compare the reaction of 2-aminopyridine with diethyl malonate (VI-201).) Neither 2-amino-3,5-dihalopyridines nor 2-amino-5-nitropyridine react even at 190–200°. Acetoacetic ester under acid catalysis forms an 8-halo-4-methyl-2*H*-pyrido[1,2-a]pyrimidin-2-one (VI-199) as the final product. Rearrangement follows displacement of halogen as 2-bromopyridine reacts with quinoline 1-oxide to give 1-(2-quinolyl)-2(1*H*)-pyridone (*167*).



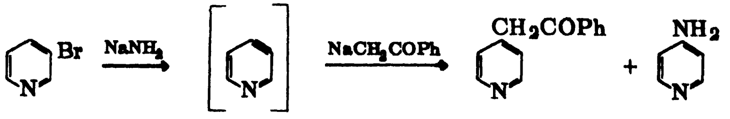
(VI-200)

(VI-199)



(VI-201)

When 3-bromopyridine is treated first with sodium amide and then with the sodio derivative of acetophenone, 4-phenacylpyridine and some 4-aminopyridine are formed (VI-203) (*358*). Levine and Leake (*343*) have suggested that this result indicates the existence of an intermediate "pyridyne" (VI-202), in analogy with the "benzyne" proposed by Roberts *et al.* (*344*). No reaction takes place when 3-bromopyridine is treated with the sodio acetophenone alone.



(VI-202)

(VI-203)

The halogen of halopyridines is unaffected by phenacyl halides, but the ring nitrogen is attacked. 3- or 3,5-Halopyridines react more rapidly than 2-chloro- or 2-bromopyridine, in accordance with (*a*) the deactivating effect of a negative substituent at 2 or 4 and (*b*) steric hindrance by substituents at 2 (*345*). 2-Chloro-5-nitropyridine loses halogen when treated with methyl sulfate and alkali, to form 1-methyl-5-nitro-2(1*H*)-pyridone (*316*). 3-Bromo-2-chloro-5-nitropyridine gives the 3-bromo analogue. 6-Chloro-2,4-dihydroxynicotinonitrile, in contrast, retains halogen when treated with methyl sulfate, to form first 6-chloro-3-cyano-4-hydroxy-1-methyl-2(1*H*)-pyridone (*182*).

2-Chloropyridine fails to give the 4-ethyl derivative in the Wibaut-Arens reaction (zinc and acetic anhydride) in contrast to pyridine itself (*237*).

2- and 3-Chloropyridines form molecular complexes with phenols. The halopyridines react to a greater extent than 2- or 3-aminopyridine, apparently as a result of their more hydrophobic nature (*346*).

h. Formation of Organometallic Compounds

Early attempts to prepare Grignard reagents from halopyridines failed, and careful study of 2-halopyridines under what are normally considered forcing conditions indicated inertness of the halogen toward magnesium (*347*). Overhoff and Proost (*348*) discovered that Grignard reagents can be obtained by the "entrainment method," *i.e.*, admixture of the halopyridine with a Grignard reagent from a reactive halide, such as ethyl bromide, and excess magnesium. Both 2- and 3-bromopyridines react, and the resulting Grignard reagents undergo typical reactions. Thus from 2-bromopyridine, ethyl bromide, magnesium, and benzaldehyde may be obtained α-phenyl-2-pyridinemethanol. Using this general technique, the reaction has been extended to benzophenone, acetophenone (*349,350*), picolinonitrile or ethyl picolinate to give bis(2-pyridyl) ketone (*351*), and benzonitrile to give 2-benzoylpyridine. Two moles of the Grignard reagent react with ethyl benzoate to give bis(2-pyridyl)phenylcarbinol and both halogens of 2,6-dibromopyridine react to form α,α′-diphenyl-2,6-pyridinedimethanol (*352*). The Grignard reagents react with a variety of phosphorus and arsenic halides to give pyridine-substituted derivatives of these elements (*319,353*).

Halopyridines react with organolithium compounds to give pyridyllithium derivatives, which in turn may react much like the Grignard reagents. Thus 2-bromo-3-picoline with butyllithium forms a reactive intermediate which with benzaldehyde leads to 3-methyl-α-phenyl-2-pyridinemethanol (*66*). 2-Bromopyridine and butyllithium are similarly employed with chlorobenzaldehydes; the phenyl chlorine remains intact throughout. Butyraldehyde reacts with the pyridyllithium from 2-bromo- or 6-bromo-3-picoline and butyllithium to form the corresponding carbinols (*354*). The complex side reactions are discussed by Gilman and Spatz (*355*). 3-Pyridyllithium reacts with 3-bromopyridine to give 3,3′-bipyridine. Only one halogen of either 3,5- or 2,6-dibromopyridine reacts to form the lithium derivative. (Compare the formation of di-Grignard reagents.) Accordingly, the dibromopyridines may be converted to the corresponding bromo acids by treatment with butyllithium followed by carbonation. Butyllithium furnishes the expected 3,4,6-triphenyl-2-pyridyllithium with 2-bromo-3,4,6-triphenylpyridine (*356*), but lithium metal reduces this halopyridine to 2,4,5-triphenylpyridine (*357*).

The preparation and reactions of magnesium, lithium, and other organometallic pyridine derivatives are fully discussed in Chapter VII.

4. Compounds of Polyvalent Iodine

3-Iodopyridines react in a manner analogous to iodobenzenes to from higher valent iodine derivatives. 3-Iodopyridine dichloride is prepared in quantitative yield by passing chlorine into a cold solution of 3-iodopyridine in chloroform (*278,279*). The method is generally applicable, and the substituted analogues listed in Table VI-16 (p. 400) were prepared in this manner.

These 3-iodopyridine dichlorides behave like iodobenzene dichloride. With dilute alkali 2-chloro-5-iodopyridine dichloride is transformed to 2-chloro-5-iodosopyridine (*279,280*), which disproportionates when treated with steam to give a mixture of 2-chloro-5-iodoxypyridine and 2-chloro-5-iodopyridine. A similar hydrolysis of 2-acetamino-5-iodopyridine dichloride leads to 2-acetamino-5-iodosopyridine (*280*).

2-Iodopyridine does not give a dichloride (*209,280*).

C. SIDE-CHAIN HALOGEN DERIVATIVES

1. Preparation and Properties

a. Halogenation of Saturated Side-Chains

Halogenation of the side-chain concurrently with nuclear halogenation has already been discussed (p. 304). The following examples, in which nuclear halogenation did not occur, are reported in the same study: 2-trichloromethylpyridine, 2,4-bis(trichloromethyl)pyridine, and 2,4,6-tris(trichloromethyl)pyridine. In each case the corresponding picoline, lutidine, or collidine was chlorinated in aqueous solution (*8*). 2,6-Bis(trichloromethyl)pyridine has been prepared from 2,6-lutidine by passing thionyl chloride into the melted hydrochloride (*359*). Chlorination of 2-picoline in glacial acetic acid containing potassium acetate gives 2-trichloromethylpyridine and 2-dichloromethylpyridine with no monochloro, even when less than one mole of chlorine is employed (*360*).

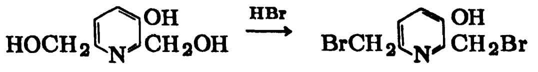
Bromination of 3-picoline in hydrochloric acid at 150° gives 3-bromomethylpyridine (*361*), while 5-(1-bromoethyl)-2-picoline results upon brominating 5-ethyl-2-picoline (*362*). Bromine in carbon disulfide converts ethyl 2-pyridineacetate to ethyl α-bromo-2-pyridineacetate (*363*). The methyl group of ethyl 6-chloro-2-methylnicotinate is brominated by *N*-bromosuccinimide to give ethyl 2-bromomethyl-6-chloronicotinate (*79*). Bromine in glacial acetic acid gives almost quantitatively 4-(α-bromophenacyl)pyridine from 4-phenacylpyridine (*364*).

2-Bromomethylpyridine and 2,6-bis(bromomethyl)pyridine are formed by treating the corresponding alkyllithium compounds with bromine (*385*). The low yields obtained may be accounted for by the instability of these halopyridines.

b. Displacement of Oxygen or Halogen

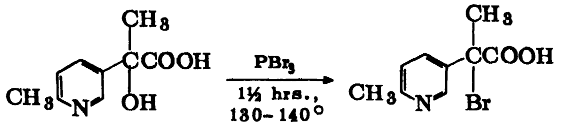
Treatment of 3-pyridineethanol with hydrochloric acid gives 3-(2-chloroethyl)pyridine (*365*), and 4-(2-chloroethyl)pyridine may be prepared in a similar manner (*276*). Thionyl chloride or a phosphorus halide is the usual reagent, however, and compounds so prepared are listed in Table VI-17 (pp. 401 ff.).

Bromine is introduced similarly; the usual reagents are strong aqueous hydrobromic acid or hydrogen bromide in an acidic solvent. Thus 2-bromomethyl- and 4-bromomethylpyridines have been derived from the respective pyridinemethanols (*366*). An interesting example illustrating the relative inertness of a nuclear hydroxyl at position 3 is the preparation of 2,6-bis(bromomethyl)-3-pyridinol (VI-205) from 3-hydroxy-2,6-pyridinedimethanol (VI-204) (*367*). In cases where hydrogen bromide fails, phosphorus tribromide is sometimes successful. Thus, while no α-bromo-6,α-dimethyl-3-pyridineacetic acid (VI-208) could be obtained from 6,α-dimethyl-3-pyridineglycolic acid (VI-207) with aqueous hydrobromic acid, the transformation was accomplished with phosphorus tribromide at 130° (*368*). Replacement of hydroxyl once removed from the ring appears to take place more readily (although with danger of dehydration or dehydrohalogenation); thus α-bromo-2-pyridinepropionic acid may



(VI-206)

(VI-204) (VI-205)

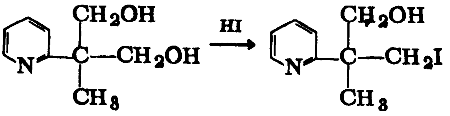


(VI-209)

(VI-207) (VI-208)

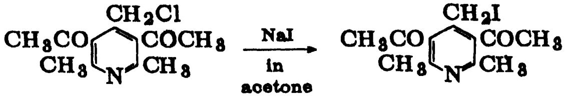
be prepared by treating 2-pyridinelactic acid with either hydrogen bromide or phosphorus tribromide (*369*). Other bromoalkylpyridines so prepared are listed in Table VI-17 (pp. 401 ff.).

Hydriodic acid is the usual reagent for replacement of alcoholic hydroxyl with iodine. When 2-pyridineethanol is heated with aqueous hydriodic acid, 2-(2-iodoethyl)pyridine is formed (*370,371*). This compound is rather unstable as the free base (it gives the quaternary iodide), and must be isolated and kept as a salt (*e.g.*, the picrate). In the case of compounds with several replaceable hydroxyls, one or more may replace with difficulty. Such is the case for VI-210; after ten hours with hydriodic acid β-iodomethyl-β-methyl-2-pyridineethanol (VI-211) is the main product (*372*). Contrast to this, however, the conversion of β,β-bis(hydroxymethyl)-4-pyridineethanol to 4-[1,1-bis(iodomethyl)-2-iodoethyl]pyridine by hydriodic acid and red phosphorus (*373*). Other examples are listed in Table VI-17. (*Cf.* Chapter XIII, Table XIII-8.)



(VI-210) (VI-211) (VI-212)

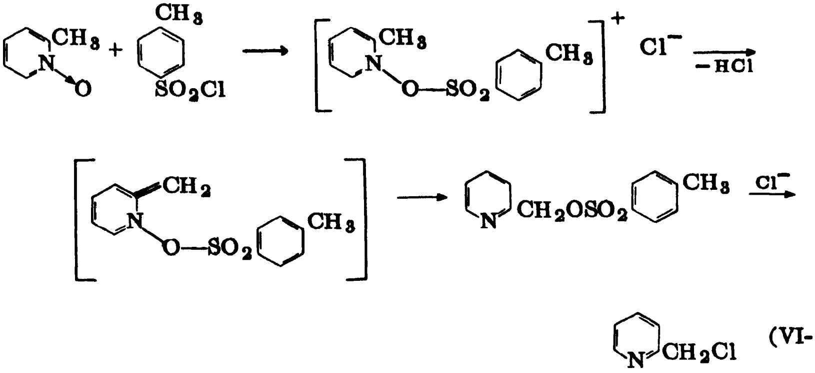
Analogous to the replacement of hydroxyl by halogen is the exchange of one halogen for another. Two trifluoromethylpyridines, 2,4-bis(trifluoromethyl)pyridine and 2,6-bis(trifluoromethyl)pyridine, have been derived from the corresponding trichloromethylpyridines by treating with hydrogen fluoride at elevated temperatures (*8*). 2-(Trifluoromethyl)pyridine has been obtained from the reaction of trifluoroacetonitrile with butadiene at 475° (*339*). When 3,5-diacetyl-4-chloromethyl-2,6-lutidine (VI-213) is refluxed with sodium iodide in acetone, the corresponding iodomethyl compound (VI-214) results (*391*). 4-(2-Iodoethyl)pyridine is transformed into 4-(2-chloroethyl)pyridine by hydrochloric acid with silver chloride (*390*).



(VI-213) (VI-214) (VI-215)

Related to the displacement of hydroxyl is the preparation of 3-(α-chlorovinyl)pyridine from methyl 3-pyridyl ketone (3-acetopyridine) by treatment with phosphorus pentachloride in benzene (*392*).

Halogen is introduced into the side chain via a rearrangement and displacement when 2-picoline 1-oxide is treated with *p*-toluenesulfonyl chloride. Matsumura (*18*) has proposed a mechanism (VI-216) for this reaction. Under similar conditions 3-picoline 1-oxide gives 5-methyl-3-pyridinol rather than 3-chloromethylpyridine.



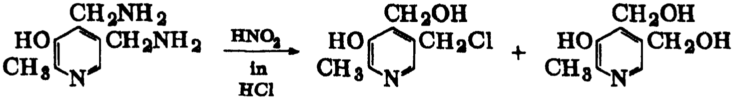
(VI-216)

Dehydration may occur under conditions for hydroxyl displacement. For example, when α-(trichloromethyl)-2-pyridineethanol is treated with phosphorus pentachloride, 2-(3,3,3-trichloropropenyl)-pyridine is obtained (*393*). Dehydration is similarly observed when 4,6-dimethyl-α-(trichloromethyl)-2-pyridineethanol is treated with phosphorus pentachloride and red phosphorus (*394*).

c. From Side-Chain Amines

Aminoalkylpyridines react with nitrous acid in concentrated hydrohalic acids to give the corresponding haloalkylpyridines. Thus, when 2-aminomethylpyridine is treated with sodium nitrite in concentrated hydrochloric acid, 2-chloromethylpyridine is formed (its presence in good yield was shown by subsequent reactions without isolation). The isolated product is said to be unstable (*395*). 3,4-Bis(aminomethyl)pyridine gives 3,4-bis(chloromethyl)pyridine when similarly treated (*396*). Conversion of the aminomethyl to hydroxymethyl is a possible side reaction, seen in the formation of 5-hydroxy-6-methyl-3,4-pyridinedimethanol (VI-219) along with 5-

chloromethyl-3-hydroxy-2-methyl-4-pyridinemethanol (VI-218) from 4,5-bis(aminomethyl)-2-methyl-3-pyridinol (VI-217) (*376*).

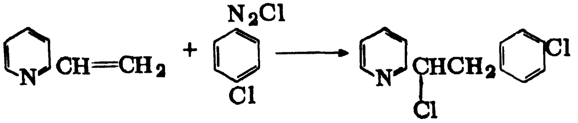


(VI-217) (VI-218) (VI-219) (VI-220)

d. Addition of Halogen or Hydrogen Halide to Unsaturated Side-Chain

Addition of chlorine or bromine to a side-chain double bond generally affords the corresponding dihalide (Table VI-18, p. 404). For example, when 2-stilbazole is treated with chlorine in carbon tetrachloride, the chlorine molecular addition compound of 2-(α,β-dichlorophenethyl)pyridine results (*397*). With bromine a 95% yield of 2-(α,β-dibromophenethyl)pyridine is obtained (*398*). By contrast, however, 4-stilbazole forms a perbromide with bromine; the starting material is regenerated upon treatment with potassium hydroxide (*364*). This perbromide forms α-(or β-)bromo-4-stilbazole when refluxed with glacial acetic acid.

The addition of hydrogen chloride or hydrogen bromide to an unsaturated side-chain to give a monohalo derivative has been reported (*400,409*), but the direction of addition was not ascertained in this early work. From later studies on the reaction of *p*-chloro-(as well as *p*-nitro- and *p*-methyl-)benzenediazonium chloride with 2-vinylpyridine under Meerwein reaction conditions (*234*) to give 2-(α,*p*-dichlorophenethyl)pyridine (VI-221), it might well be assumed



(VI-221) (VI-222)

that halogen would enter adjacent to the pyridine nucleus. This is the case when 2-pyridineacrylic acid adds hydrogen bromide to give β-bromo-2-pyridinepropionic acid (*393*).

e. Introduction of a Halogenated Side-Chain

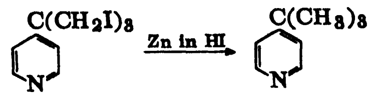
One of the earliest observed reactions of 2- or 4-picoline is the condensation with an aldehyde to form an alcohol. Chloral readily condenses with 2-picoline to form α-(trichloromethyl)-2-pyridineethanol (*413,414*). The reaction is best accomplished by simply warming the reactants on the steam bath, although amyl acetate may be employed as a solvent (*410,415*). Upon treatment with phosphorus pentachloride the alcohol is dehydrated to the corresponding olefin; for the above example, 2-(3,3,3-trichloropropenyl)-pyridine (*410*). Zinc chloride has been used as a catalyst with 4-picoline to furnish 16–18% of α-(trichloromethyl)-4-pyridineethanol (*392,416,417*). Only one methyl group of 2,6-lutidine reacts (*418*). 2,4,6-Collidine behaves similarly, and gives 4,6-dimethyl-α-(trichloromethyl)-2-pyridineethanol, even with excess chloral (*419*) or when heated with chloral in amyl acetate (*394*). The corresponding products have been prepared in the same manner from 5-ethyl-2-picoline (aldehyde collidine) (*420*) and 6-phenyl-2-picoline (*421*).

2. Reactions

a. Reduction

Side-chain halogen is smoothly removed by chemical reduction. Thus zinc in acetic acid has been used to remove halogen from 2-(1-chlorobutyl)-3-picoline and 6-(1-chlorobutyl)-3-picoline to form the corresponding butylpicolines (*354*), and from 5-(α-chlorobenzyl)-2-phenylpyridine (*377,423*) and 2-(α-chlorobenzyl)-3-picoline (*66*).

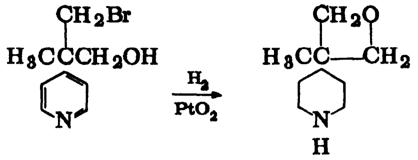
Halogen on carbons one or more removed from the ring may be removed by zinc in mineral acid. Thus 6-(2-bromoethyl)-2-picoline is reduced to 6-ethyl-2-picoline by zinc in acid (*380*), and halogen is similarly removed from 2-(2-iodoethyl)-pyridine, 2-(1-iodo-*i*-propyl)-pyridine (*370*), and 2-(2-iodobutyl)pyridine (*378*). In sharp contrast, however, is the formation of 2-(1-butenyl)pyridine from 2-(2-chlorobutyl)pyridine by the same reagent. 2-Bromomethyl-3-pyridinol is reduced to 2-methyl-3-pyridinol by zinc in hydrobromic acid (*387*), and VI-223 is converted to 4-*t*-butylpyridine by zinc in hydriodic acid (*373*).



(VI-223)

(VI-224)

Side-chain halogen may also be removed by hydrogenation over noble metal catalysts, although with greater difficulty than nuclear halogen, as already noted (p. 347). Thus the hydrobromide of 4,5-bis(bromomethyl)-2-methyl-3-pyridinol is reduced to 2,4,5-trimethyl-3-pyridinol (Pd-$BaCO_3$) (*424*), and 2-bromomethyl-6-methyl-3-pyridinol is similarly reduced (PtO_2, at room temperature) (*296*). The pyridine ring undergoes reduction and a cyclic ether is formed when VI-225 is hydrogenated (*386*). Halogen remains intact as the ring of α-(trichloromethyl)-4-pyridineethanol is reduced under similar conditions (*425*). Partial removal of halogen from this latter compound may be achieved by refluxing with zinc in ethanol and acetic acid. Stannous chloride in acetone removes one halogen of 2-trichloromethylpyridine to form 2-dichloromethylpyridine (*360*).



(VI-225)

(VI-226)

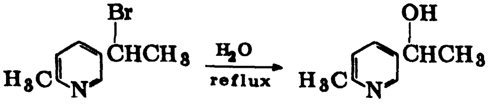
b. Dehalogenation and Dehydrohalogenation

Hydrogen halide is readily removed from side-chain halopyridines by treating with alkali. 3-Vinylpyridine is formed when 3-(1-chloroethyl)pyridine is treated with alcoholic potassium hydroxide (*375*). The same reagent converts 3-(1-chlorovinyl)pyridine to 3-ethynylpyridine (*392*). Halogen may be removed from carbon β to the ring by similar treatment, as seen in the conversion of 3-(2-chloroethyl)-4-picoline to 3-vinyl-4-picoline (*143*) and 4-(2-iodoethyl)-pyridine to 4-vinylpyridine (*276*) by the same reagents. Elimination proceeds quite readily for the bromophenethylpyridines; this reaction has found considerable use in the preparation of stilbazoles and their conversion to pyridylphenylacetylenes via the dibromide.

In a comparative study of methods for removing halogen from 2-(α,β-dibromophenethyl)pyridine (2-stilbazole dibromide) (*397*), sodium methoxide appeared the reagent of choice for preparing bromo-2-stilbazole (bromine position not certain). Potassium iodide in boiling alcohol converts the dibromide to 2-stilbazole, while alkali in 95% alcohol gives some stilbazole along with bromostilbazole. Good yields of 2-phenylethynylpyridine are obtained by treating 2-(α,β-dibromophenethyl)pyridine with potassium hydroxide in refluxing alcohol. 2,6-Bis(phenylethynyl)pyridine is prepared similarly (*398*). 2-(α,β-Dibromo-*o*-nitrophenethyl)pyridine and the corresponding dichloro compound react similarly; the latter loses a single mole of hydrogen chloride on treatment with pyridine (*399*). An almost quantitative yield of 4-phenylethynylpyridine results from 4-(β-bromostyryl)pyridine (*364*). 2-Stilbazole is formed as expected from 2-(β-bromophenethyl)pyridine by treating with alkali (*409*).

c. *Hydrolysis*

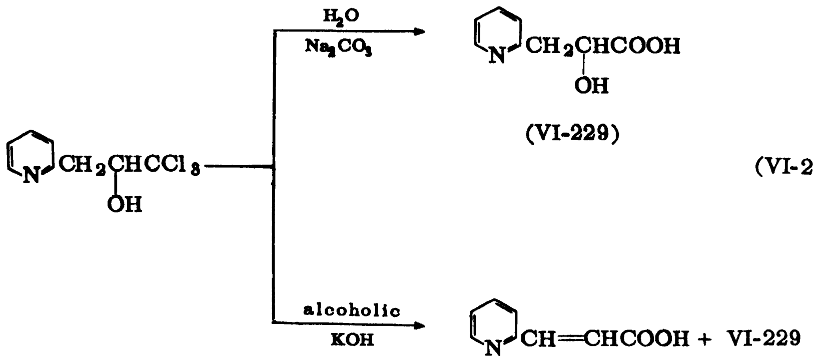
Halogen on carbon attached to the ring is fairly labile, and is readily hydrolyzed by boiling with water or by dilute alkali. Refluxing in water converts 5-(1-bromoethyl)-2-picoline to the corresponding pyridinealkanol (VI-227) (*362*). 2-Bromomethyl-6-methyl-



(VI-228)

(VI-227)

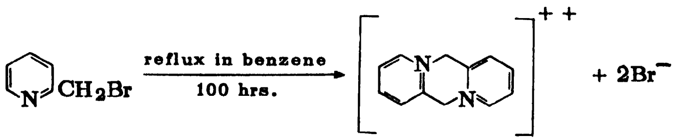
3-pyridinol suffers hydrolysis upon attempted recrystallization from water (*387*). 3-Amino-5-aminomethyl-4-bromomethyl-2-picoline (*175*) and 4,5-bis(bromomethyl)-2-methyl-3-pyridinol (*262*) are similarly hydrolyzed by boiling water. The halogens of 2-trichloromethylpyridine or 2,6-bis(trichloromethyl)pyridine require refluxing for eight hours with 30% sulfuric acid for hydrolysis to the corresponding carboxylic acids (*359,360*). The latter halopyridine is converted to methyl 6-(trichloromethyl)picolinate by sulfuric acid in methanol. When 2-dichloromethylpyridine is heated in 30% sulfuric acid or treated with silver nitrate in aqueous alcohol, it hydrolyzes to the corresponding aldehyde (*360,422*). More drastic conditions are necessary to hydrolyze halogen on carbon farther removed from the ring, and 3-(2-chloroethyl)-2-picoline must be heated to 160° with water to effect hydrolysis (*148*). Dehydration is noted as a side reaction in the preparation of 2-pyridinelactic acid (VI-229) from α-(trichloromethyl)-2-pyridineethanol by treatment with alcoholic alkali (*413*). This may be avoided, and VI-229 obtained in good yield, by hydrolyzing with aqueous sodium carbonate (*410*). (*Cf.* Chapter XIII for the preparation of pyridine alcohols from halides.)



(VI-230)

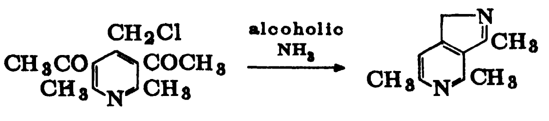
d. Metathesis

Side-chain halogen undergoes the normal metathetical reactions of haloalkylamines. 2-Bromomethylpyridine self-condenses when refluxed in benzene (VI-231), while the 4-bromomethyl analogue



(VI-231)

forms polymer (by self-condensation) under these conditions (*366*). (*Cf.* Chapter III, p. 72.) The aminomethyl derivative resulting from amination of 3,5-diacetyl-4-chloromethyl-2,6-lutidine (VI-232) cyclizes (*391*), and an analogous cyclization is observed upon amination or

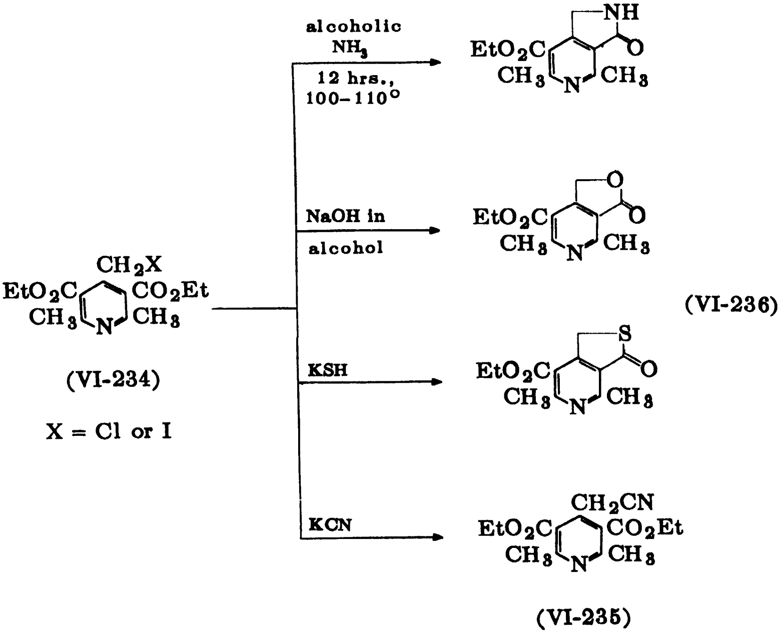


(VI-233)

hydrolysis of VI-234, or attempted conversion of the corresponding iodomethyl compound to the thiol. Halogen on carbon β to the ring reacts smoothly with secondary amines in methanol to form aminoalkylpyridines (*371,374,382*). 3-(2-Chloroethyl)pyridine reacts with trimethylamine in methanol to form 3-(2-dimethylaminoethyl)pyridine in 54% yield, indicating a preferred tendency for the elimination of a methyl group (as compared to the elimination of the pyridylethyl group) from the quaternary salt (*365*). 4-(2-Iodoethyl)pyridine, 6-(2-bromoethyl)-2-picoline, and similar halopyridines give quaternary pyridinium salts upon standing or warming (*378,382,390*). 6-(2-Bromoethyl)-2-picoline reacts with ammonia in ethanol to form 6-(2-aminoethyl)-2-picoline (*381*).

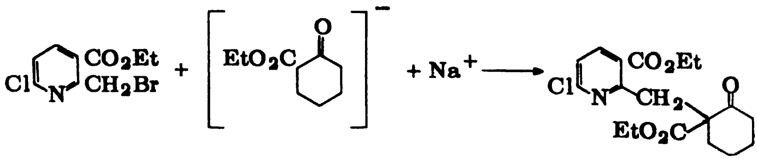
The halogen of 4,5-bis(bromomethyl)-2-methyl-3-pyridinol is replaced by acetoxyl when it is treated with silver acetate and potassium acetate in acetic acid (*424*). 3-Pyridinemethyl nicotinate is formed from 3-chloromethylpyridine and sodium nicotinate (*426*).

Side chain halogen may be displaced by cyano upon treating with potassium cyanide. Thus VI-234 (X = I) reacts to form VI-235 (*391*), while 3-chloromethylpyridine forms 3-pyridineacetonitrile (*338*).

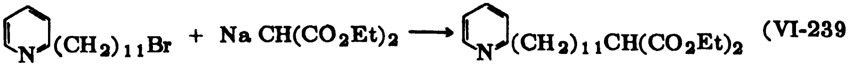


e. C-Alkylation

2-Chloromethylpyridine and 4-bromomethylpyridine react with the sodio derivative of benzoylaminomalonic ester to give, after hydrolysis, *dl*-2-pyridine- and *dl*-4-pyridinealanines (*379*). Ethyl 2-bromomethyl-6-chloronicotinate alkylates the sodio derivative of malonic ester or 2-carbethoxycyclohexanone similarly (VI-237), illustrating the relative inertness of nuclear halogen in reactions of this sort (*79*). 2-(11-Bromohendecyl)pyridine reacts with sodio diethyl malonate to give the expected product (VI-238), an intermediate needed to prepare a pyridine analogue of chaulmoogric acid (*383*).



(VI-237)



(VI-239)

(VI-238)

The properties of side-chain halogen derivatives of pyridine are summarized in Tables VI-15, VI-17, VI-18, and VI-19 (pp. 398 ff.).

D. TABLES

TABLE VI-1. Pyridine-Halogen Molecular Addition Compounds

Compound	Melting point, °C.	Ref.
$C_5H_5N \cdot Cl_2$	47	116,114
$C_5H_5N \cdot Br_2$	94–95	118
	62–63	114
$C_5H_5N \cdot Br_4$	58.5	118
$C_5H_5N \cdot Br_x$	approx. 100	57
$(C_5H_5N)_2 \cdot I_2$ (?)	53	119
$C_5H_5N \cdot I_2$	62	119
$C_5H_5N \cdot I_4$	85	120
$C_5H_5N \cdot ICl$	132	129
	134	114,122
$C_5H_5N \cdot BrCl$	107–8	114
$C_5H_5N \cdot IBr$	116–17	114
$C_5H_5N \cdot ICl_3$		122
$C_5H_5N \cdot ClO_2$		123

TABLE VI-2. Salts of Pyridine Molecular Addition Compounds

Compound	Physical properties	Ref.
$(C_5H_5N \cdot HCl)_2 \cdot Cl_2$	in solution only	57
$C_5H_5N \cdot HCl \cdot Br_x$	solid, but not isolated	57
$C_5H_5N \cdot HCl \cdot I_2$	m.p. 150°	57
$C_5H_5N \cdot HCl \cdot ICl$	m.p. 180°	122,126,129
	m.p. 183°	130
$C_5H_5N \cdot HCl \cdot ICl_3$		122,126
$(C_5H_5N \cdot HCl \cdot ICl)(C_5H_5N \cdot HCl \cdot ICl_3)$		118
$C_5H_5N \cdot HCl \cdot BrCl$	m.p. 51°	118
$C_5H_5N \cdot HBr \cdot Br_x$	m.p. 101–3°	124
$(C_5H_5N \cdot HBr)_2 \cdot Br_2$	m.p. 88° and 93°	118
$C_5H_5N \cdot HBr \cdot Br_2$	"low melting"	47,125
	m.p. 132–34°	124
$(C_5H_5N \cdot HBr \cdot Br)(C_5H_5N \cdot HBr \cdot Br_2)$	m.p. 125°	118
$(C_5H_5N \cdot Br_2)_2 \cdot HBr$ (?)	m.p. 126° (decomp.)	117
$C_5H_5N \cdot HBr \cdot IBr$ (or $C_5H_5N \cdot HI \cdot Br_2$)	m.p. 172–75°	118
$C_5H_5N \cdot HBr \cdot Br_2 \cdot 2H_2O$	m.p. 118–20°	118,125
$(C_5H_5N \cdot HI \cdot Cl_2)(C_5H_5N \cdot HI \cdot Cl_4)$	m.p. 176°	118
$C_5H_5N \cdot HI \cdot I$	m.p. 182–92°	131
$C_5H_5N \cdot HI \cdot I_4$	m.p. 78–85°	131
	m.p. 89°	132
$C_5H_5N \cdot HI \cdot I_6$	m.p. 63–64°	131

TABLE VI-3. Halogen Addition Compounds of 1-Alkylpyridinium Salts

Compound			Melting point, °C.	Ref.
1-Alkyl	Anion	Halogen		
CH_3-	Br^-	IBr	90	116
CH_3-	Cl^-	ICl	81-82	128
CH_3-	Cl^-	ICl_3	185	118
			179-80	116
CH_3-	Br^-	$\frac{1}{2}Br_2$	82-83	118
CH_3-	Br^-	Br_2	66	118
CH_3-	I^-	$\frac{1}{2}I_2$	91.5	120
CH_3-	I^-	I_2	50	120
CH_3-	I^-	$2I_2$	47.5	120,131
CH_3-	I^-	$3I_2$	26	120,131
CH_3-	Cl^-	ICl_3	123	118
C_2H_5-	Br^-	Br_2	35	118
C_2H_5-	Br^-	$Br_2 \cdot 2H_2O$	15	118
C_2H_5-	Br^-	IBr	25-26	118
C_2H_5-	I^-	I_2	51	120,131
C_2H_5-	I^-	I_4	83	131

TABLE VI-4. Molecular Addition Compounds of Substituted Pyridines

Compound	Physical properties	Ref.
2-PyMe • Br_2	m.p. approx. 95°	57
2-PyMe • HCl • Br_2	liquid	57
3-PyMe • HCl • Br_2		57
4-PyMe • HCl • Br_2		57
2-PyNH_2 • $2Br_2$	not isolated from reaction mixture	127
2-Amino-5-iodopyridine periodide	m.p. 144-46°	101
6-Amino-3-nitro-2-picoline dibromide	m.p. 230°	36
Nicotinic acid perbromide		83

TABLE VI-5. Polyhalopyridines from Halopyridinols

Starting material	Product	Reagent	Ref.
6-Chloro-2-pyridinol	2,6-dichloropyridine	$POCl_3$	29
3,5-Dichloro-2-pyridinol	2,3,5-trichloropyridine	PCl_5-$POCl_3$	32
3,5-Dichloro-4-pyridinol	3,4,5-trichloropyridine	PCl_5-$POCl_3$	32
4,5-Dichloro-2-pyridinol	2,4,5-trichloropyridine	$POCl_3$	26
3,4,5-Trichloro-2-pyridinol	2,3,4,5-tetrachloropyridine	PCl_5	10
3,5,6-Trichloro-2-pyridinol	2,3,4,6-tetrachloropyridine	PCl_5-$POCl_3$	29
3,5-Dibromo-2-pyridinol	3,5-dibromo-2-chloropyridine	PCl_5	32
		PCl_5-$POCl_3$	29
3,5-Dibromo-4-pyridinol	3,5-dibromo-4-chloropyridine	PCl_5	32
3,5-Dibromo-4-pyridinol	3,4,5-tribromopyridine	$POBr_3$	138
3,5-Diiodo-2-pyridinol	2-chloro-3,5-diiodopyridine	PCl_5	32,99
3,5-Diiodo-4-pyridinol	4-chloro-3,5-diiodopyridine	PCl_5-$POCl_3$	32
3,5-Dibromo-6-methyl-2-pyridinol	3,4,5-tribromo-2-picoline	$POBr_3$	92
3,5-Diiodo-2,6-dimethyl-4-pyridinol	4-chloro-3,5-diiodo-2,6-lutidine	PCl_5-$POCl_3$	104

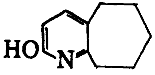
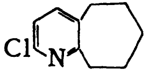
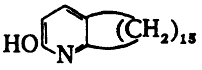
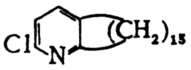
TABLE VI-6. Polyhalopyridines from 1-Alkylhalopyridones

Starting material	Product	Reagent	Ref.
5-Chloro-1-methyl-2(1*H*)-pyridone	2,5-dichloropyridine	$COCl_2$	140
5-Chloro-1-benzyl-2(1*H*)-pyridone	2,5-dichloropyridine	$COCl_2$	154
5-Bromo-1-methyl-2(1*H*)-pyridone	5-bromo-2-chloropyridine	$COCl_2$	140
6-Bromo-1-methyl-2(1*H*)-pyridone	2,6-dibromopyridine	PBr_3-$POBr_3$	188
5-Iodo-1-methyl-2(1*H*)-pyridone	2-chloro-5-iodopyridine	$COCl_2$	140,154
3,5-Dichloro-1-methyl-2(1*H*)-pyridone	2,3,5-trichloropyridine	PCl_5-$POCl_3$	189
		PCl_5	140
		$COCl_2$	140
3,5-Dibromo-1-methyl-2(1*H*)-pyridone	3,5-dibromo-2-chloropyridine	$COCl_2$	140
3,5-Dibromo-1-methyl-2(1*H*)-pyridone	2,3,5-tribromopyridine	PBr_5-$POBr_3$	189
3,5-Dibromo-1-(2-hydroxyethyl)-2(1*H*)-pyridone	2,3,5-tribromopyridine	PBr_5-$POBr_3$	428
3,5-Diiodo-1-methyl-2(1*H*)-pyridone	2-chloro-3,5-diiodopyridine	$COCl_2$	140
		PCl_5	99
3,5,6-Tribromo-1-methyl-2(1*H*)-pyridone	2,3,5,6-tetrabromopyridine	PBr_5	73

TABLE VI-7. Polyhalopyridines from Halopyridinediols

Starting material	Product	Reagent	Ref.
3-Chloro-2,4-pyridinediol	2,3,4-trichloropyridine	$POCl_3$	31
5-Chloro-2,4-pyridinediol	2,4,5-trichloropyridine	PCl_5-$POCl_3$	26
3-Bromo-2,4-pyridinediol	3-bromo-2,4-dichloropyridine	$POCl_3$	31
5-Bromo-2,4-pyridinediol	5-bromo-2,4-dichloropyridine	$POCl_3$	31
3-Chloro-2,4-pyridinediol	2,4-dibromo-3-chloropyridine	$POBr_3$	53
5-Chloro-2,4-pyridinediol	2,4-dibromo-5-chloropyridine	$POBr_3$	26
3-Bromo-2,4-pyridinediol	2,3,4-tribromopyridine	$POBr_3$	31,53
5-Bromo-2,4-pyridinediol	2,4,5-tribromopyridine	$POBr_3$	53
3-Bromo-5-chloro-2,4-pyridinediol	3-bromo-2,4,5-trichloropyridine	$POCl_3$	26
5-Bromo-3-chloro-2,4-pyridinediol	5-bromo-2,3,4-trichloropyridine	$POCl_3$	31
3-Bromo-5-chloro-2,4-pyridinediol	2,3,4-tribromo-5-chloropyridine	$POBr_3$	26
5-Bromo-3-chloro-2,4-pyridinediol	2,4,5-tribromo-3-chloropyridine	$POBr_3$	31

TABLE VI-8. Halopyridines from Alkylpyridinols and Arylpyridinols

Starting material	Product	Reagent	Ref.
6-Methyl-2-pyridinol	6-bromo-2-picoline	$POBr_3$	92
5-Methyl-2-pyridinol	6-bromo-3-picoline	$POBr_3$	87
3-Methyl-2-pyridinol	2-chloro-3-picoline	PCl_5	281
4-Methyl-2-pyridinol	2-chloro-4-picoline	PCl_5	197
6-Propyl-2-pyridinol	6-chloro-2-propylpyridine	PCl_5-$POCl_3$	198
6-*i*-Butyl-2-pyridinol	6-chloro-2-*i*-butylpyridine	PCl_5-$POCl_3$	192
2,6-Dimethyl-4-pyridinol	4-chloro-2,6-lutidine	PCl_5-$POCl_3$	194
5,6-Dimethyl-2-pyridinol	6-chloro-2,3-lutidine	PCl_5-$POCl_3$	195
4,6-Dimethyl-2-pyridinol	6-chloro-2,4-lutidine	PCl_5	196
6-Ethyl-4-methyl-2-pyridinol	6-chloro-2-ethyl-4-picoline	PCl_5-$POCl_3$	144
6-*i*-Propyl-5-methyl-2-pyridinol	6-chloro-2-*i*-propyl-3-picoline	PCl_5-$POCl_3$	193
6,7-Dihydro-5*H*-1-pyrindine-2-ol	2-chloro-6,7-dihydro-5*H*-1-pyrindine	PCl_5-$POCl_3$	190
		PCl_5-$POCl_3$	191
		$POCl_3$	170

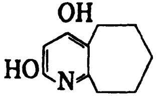
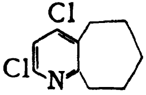
4,5,6-Trimethyl-2-pyridinol	6-chloro-2,3,4-trimethylpyridine	PCl_5	199
3,6-Dimethyl-2,4-pyridinediol	4,6-dichloro-2,5-lutidine	PCl_5-$POCl_3$	195
3-Ethyl-4-methyl-2,6-pyridinediol	2,6-dichloro-3-ethyl-4-picoline	PCl_5-$POCl_3$	201
6-Ethyl-3-methyl-2,4-pyridinediol	2,4-dichloro-6-ethyl-3-picoline	$POCl_3$	200
6,7-Dihydro-5*H*-2-pyrindine-1,3-diol	1,3-dichloro-6,7-dihydro-5*H*-2-pyrindine	PCl_5-$POCl_3$	145
6,7-Dihydro-5*H*-1-pyrindine-2,4-diol	2,4-dichloro-6,7-dihydro-5*H*-1-pyrindine	$PhPOCl_2$	454
4-Ethyl-6,7-dihydro-5*H*-2-pyrindine-1,3-diol	1,3-dichloro-4-ethyl-6,7-dihydro-5*H*-2-pyrindine	$POCl_3$	145
5,6,7,8-Tetrahydroquinoline-2,4-diol	2,4-dichloro-5,6,7,8-tetrahydroquinoline	$POCl_3$	146
		$POCl_3$	56
6-Phenyl-2-pyridinol	6-chloro-2-phenylpyridine	$POCl_3$	147
2,6-Diphenyl-4-pyridinol	4-chloro-2,6-diphenylpyridine	$POCl_3$	273
5-Methyl-4,6-diphenyl-2-pyridinol	6-chloro-3-methyl-2,4-diphenylpyridine	$POCl_3$	202
3-Phenyl-2,6-pyridinediol	2,6-dichloro-3-phenylpyridine	$POCl_3$	40
3-(*p*-Chlorophenyl)-2,6-pyridinediol	3-(*p*-chlorophenyl)-2,6-dichloropyridine	$POCl_3$	140
3-Phenyl-2,6-pyridinediol	2,4,5,6-tetrachloro-3-phenylpyridine	$POCl_3$	40

TABLE VI-9. Halonitropyridines from Nitropyridinols

Starting material	Product	Reagent	Ref.
3-Nitro-2-pyridinol	2-chloro-3-nitropyridine	$POCl_3$-PCl_5	159
5-Nitro-2-pyridinol	2-bromo-5-nitropyridine	PBr_5	150
5-Nitro-2-pyridinol	2-chloro-5-nitropyridine	$POCl_3$-PCl_5	151, 152
1-Methyl-5-nitro-2(1*H*)-pyridone	2-chloro-5-nitropyridine	$COCl_2$ in toluene or $SOCl_2$	140, 153
		$POCl_3$-PCl_5	154
1-Ethyl-5-nitro-2(1*H*)-pyridone	2-chloro-5-nitropyridine	$COCl_2$ in toluene or $SOCl_2$	140, 153
1-Benzyl-5-nitro-2(1*H*)-pyridone	2-chloro-5-nitropyridine	$COCl_2$ in toluene or $SOCl_2$	140, 153
3-Nitro-4-pyridinol	4-chloro-3-nitropyridine	$POCl_3$-PCl_5	30, 44, 155
5-Chloro-3-nitro-2-pyridinol	2,5-dichloro-3-nitropyridine	$POCl_3$-PCl_5	159
5-Chloro-3-nitro-2-pyridinol	2-bromo-5-chloro-3-nitropyridine	$POBr_3 + Br_2$	159
5-Bromo-3-nitro-2-pyridinol	5-bromo-2-chloro-3-nitropyridine	$POCl_3$-PCl_5	159
5-Bromo-3-nitro-2-pyridinol	2,5-dibromo-3-nitropyridine	$POBr_3 + Br_2$	159
6-Methyl-3-nitro-2-pyridinol	6-chloro-5-nitro-2-picoline	$POCl_3$-PCl_5	36, 157
3-Methyl-5-nitro-2-pyridinol	2-chloro-5-nitro-3-picoline	$POCl_3$	168, 169
5-Methyl-3-nitro-2-pyridinol	6-chloro-5-nitro-3-picoline	$POCl_3$	156
6-Methyl-5-nitro-2-pyridinol	6-chloro-3-nitro-2-picoline	$POCl_3$-PCl_5	36, 157
4-Methyl-3-(or-5-)-nitro-2-pyridinol	2-chloro-3-(or-5-)nitro-4-picoline	$POCl_3$-PCl_5	158
3,5-Dinitro-2-pyridinol	2-chloro-3,5-dinitropyridine	$POCl_3$-PCl_5	159
5-Chloro-3-nitro-2-pyridinol	2,5-dichloro-3-nitropyridine	$POCl_3$-PCl_5	159
5-Bromo-3-nitro-2-pyridinol	5-bromo-2-chloro-3-nitropyridine	$POCl_3$-PCl_5	159
3-Bromo-5-nitro-4-pyridinol	3-bromo-4-chloro-5-nitropyridine	PCl_5	43
2-Methyl-3,5-dinitro-4-pyridinol	4-chloro-3,5-dinitro-2-picoline	$POCl_3$	303
4,6-Dimethyl-5-nitro-2-pyridinol	6-chloro-3-nitro-2,4-lutidine	PCl_5	81
4,6-Dimethyl-3,5-dinitro-2-pyridinol	6-chloro-3,5-dinitro-2,4-lutidine	PCl_5	81
3-Bromo-4,6-dimethyl-5-nitro-2-pyridinol	5-bromo-6-chloro-3-nitro-2,4-lutidine	PCl_5	81
3-Nitro-2,4-pyridinediol	4-chloro-3-nitro-2-pyridinol and 2,4-dichloro-3-nitropyridine	$POCl_3$	68

TABLE VI-10. Halopyridines from Aminopyridines by Diazotization

Starting material	Product	Method	Yield	Ref.
2-PyNH$_2$	2-PyF	NaNO$_2$ in 30% aq. HBF$_4$	40%	204,206
		NaNO$_2$ in HBF$_4$	34%	205
		amyl nitrite in HF	30%	203
		diazotize in liquid HF	"good"	115
2-PyNH$_2$	2-PyCl	NaNO$_2$ in HCl	51%	203
		NaNH$_2$, then amyl nitrite, then HCl		203
2-PyNH$_2$	2-PyBr	Br$_2$ in HBr, then NaNO$_2$ (Craig procedure)	81%	127
2-PyNH$_2$	2-PyBr with 2,5-dibromopyridine	Craig procedure	63, 10%	216
2-PyNH$_2$	2-PyBr with 2-pyridinol	Craig procedure	37, 3%	215
2-PyNH$_2$	2-PyBr	NaNH$_2$, then amyl nitrite, then HBr		203
2-PyNH$_2$	2-PyBr	NaNO$_2$ in HBr	"poor"	203
		NaNO$_2$ in HBr with added Cu	"improved"	203
2-PyNH	2-PyI	NaNH$_2$, then amyl nitrite, then HI or KI in HOAc	65%	203,224
3-PyNH	3-PyF	NaNO$_2$ in HBF$_4$	50%	205
		ethyl nitrite in 30% aq. H$_2$SiF$_6$	36%	204
		NaNO$_2$ in 75% HF with Cu	22%	209
3-PyNH$_2$	3-PyCl	Gattermann diazotization	65%	209
		Sandmeyer diazotization	34%	209
3-PyNH$_2$	3-PyBr	Gattermann diazotization	56%	209
		Sandmeyer diazotization	30%	209
3-PyNH$_2$	3-PyI	diazotize in dilute HCl, add KI	50%	209,218, 219

(continued)

TABLE VI-10. Halopyridines from Aminopyridines by Diazotization (*continued*)

Starting material	Product	Method	Yield	Ref.
4-$PyNH_2$	4-PyCl	diazotize in HCl	100%	211
4-$PyNH_2$	4-PyF	diazotize in HF		451
4-$PyNH_2$	4-PyI	diazotize in dilute HCl with added KI	15%	218
		$NaNH_2$, then nitrite, then KI		203
4-$PyNHNO_2$	4-PyCl	boil to dryness in conc. HCl	"almost 100%"	212
		$NaNO_2$ in HCl	70%	212
4-$PyNHNO_2$	4-PyCl with 3,4,5-trichloropyridine and 4-amino-3,5-dichloropyridine	HCl (38%) in a sealed tube at 100° for 10 hours	10% 20%	220
4-$PyNHNO_2$	4-PyBr	$NaNO_2$ in HBr		142
2,5-Diaminopyridine	2,5-dichloropyridine	diazotize in HCl with Cu_2Cl_2		37
3-Amino-4-picoline	3-fluoro-4-picoline	modified Schiemann reaction	68%	210
5-Amino-3-picoline	5-fluoro-3-picoline	modified Schiemann reaction	60%	168,169
5-Amino-2-picoline	5-chloro-2-picoline	diazotize in HCl with Cu_2Cl_2	25%	222
6-Amino-2-picoline	6-chloro-2-picoline	diazotize in HCl		223
2-Amino-4-picoline	2-chloro-4-picoline	diazotize in HCl	56%	197
2-Amino-4-propylpyridine	2-chloro-4-propylpyridine	diazotize in HCl	76%	227
4-Amino-2,6-lutidine	4-chloro-2,6-lutidine	diazotize in HCl		211
4-Amino-5-ethyl-2-picoline	4-chloro-5-ethyl-2-picoline	diazotize in HCl	79%	213
6-Amino-5-ethyl-2-picoline	6-chloro-5-ethyl-2-picoline	diazotize in HCl		228
5-Amino-2-picoline	5-bromo-2-picoline	diazotize in HBr with Cu_2Br_2		222
6-Amino-2-picoline	6-bromo-2-picoline	diazotize in HOAc with KBr		92
2-Amino-3-picoline	2-bromo-3-picoline	Craig procedure	46%	87
6-Amino-3-picoline	6-bromo-3-picoline	Craig procedure		87
2-Amino-4-picoline	2-bromo-4-picoline	Craig procedure	77%	87
		diazotize in HBr		229

2-Amino-4-ethylpyridine	2-bromo-4-ethylpyridine	Craig procedure		230
2-Amino-4-propylpyridine	2-bromo-4-propylpyridine	Craig procedure	88%	227
2-Amino-4-phenylpyridine	2-bromo-4-phenylpyridine	Craig procedure		230
6-Amino-2-phenylpyridine	6-bromo-2-phenylpyridine	Craig procedure		230
5-Amino-2-picoline	5-iodo-2-picoline	diazotize in acid with KI		222
4-Amino-2-ethoxypyridine	4-chloro-2-ethoxypyridine	diazotize in HCl		26
3-Amino-4-methoxypyridine	3-chloro-4-methoxypyridine	Sandmeyer diazotization		43
5-Amino-2-methoxypyridine	5-iodo-2-methoxypyridine	diazotize in HI		101
3-Amino-2-chloropyridine	2,3-dichloropyridine	diazotize in HCl		220
2-Amino-4-chloropyridine	2,4-dichloropyridine	diazotize in HCl with Cu_2Cl_2		231
3-Amino-4-chloropyridine	3,4-dichloropyridine	Gattermann diazotization		220
2-Amino-5-chloropyridine	2,5-dichloropyridine	diazotize in HCl		34
3-Amino-5-chloropyridine	3,5-dichloropyridine	Gattermann diazotization		232
		Sandmeyer diazotization		37
2-Amino-5-chloropyridine	2-bromo-5-chloropyridine	Craig procedure	79%	87
3-Amino-2-chloropyridine	3-bromo-2-chloropyridine	diazonium salt in HBr treated with $CuSO_4$		233
		Gattermann diazotization		19
5-Amino-2-chloropyridine	5-bromo-2-chloropyridine	diazotize in dil. H_2SO_4; treat with $CuSO_4$, KBr, and copper turnings		233
5-Amino-2-chloropyridine	2-chloro-5-iodopyridine	diazotize in acid, treat with iodide		236
2-Amino-5-bromopyridine	5-bromo-2-chloropyridine	diazotize in HCl, or through the Na 2-diazotate		86
2-Amino-5-bromopyridine	2,5-bromopyridine	Craig procedure	95%	87
		diazotize in HBr	40%	229
2-Amino-5-bromopyridine	5-bromo-2-iodopyridine	diazotize in HOAc with KI		88
2-Amino-5-iodopyridine	2-chloro-5-iodopyridine	diazotize in HCl		101
2-Amino-5-iodopyridine	2-bromo-5-iodopyridine	diazotize in HBr		88
2-Amino-5-iodopyridine	2,5-diiodopyridine	diazotize in HOAc with KI		88

(continued)

TABLE VI-10. Halopyridines from Aminopyridines by Diazotization (*continued*)

Starting material	Product	Method	Yield	Ref.
2-Amino-3,5-dichloropyridine	2,3,5-trichloropyridine	diazotize in HCl		34
5-Amino-2,4-dichloropyridine	2,4,5-trichloropyridine	Gattermann diazotization	40–50%	220
2-Amino-4,6- or	2,4,6-trichloropyridine	diazotize in HCl		38
4-Amino-2,6-dichloropyridine			85%	220
3-Amino-5-bromo-2-chloropyridine	5-bromo-2,3-dichloropyridine	Gattermann diazotization	32%	159
2-Amino-3,5-dibromopyridine	3,5-dibromo-2-chloropyridine	diazotize in HCl	26%	29,238
2-Amino-3,5-dibromopyridine	3,5-dibromo-2-iodopyridine	Solution in HOAc dropped into boiling solution of KI and $NaNO_2$		88
3-Amino-2,6-diiodopyridine	2,6-diiodopyridine	diazotize in ethanol		237
3-Amino-2,4,6-trichloropyridine	2,3,4,6-tetrachloropyridine	Gattermann diazotization	75%	220
4-Amino-2,3,6-trichloropyridine	2,3,4,6-tetrachloropyridine	diazotize in HCl		220
2-Amino-3,5,6-tribromopyridine	2,3,5,6-tetrabromopyridine	diazotize in HBr		89
4-Amino-3,5-diiodo-2,6-lutidine	4-chloro-3,5-diiodo-2,6-lutidine	diazotize in HCl	48%	104
4-Amino-3,5-diiodo-2,6-lutidine	3,4,5-triiodo-2,6-lutidine	diazotize in $HI-H_2SO_4$	15%	104
2,5-Diaminopyridine	2-amino-5-iodopyridine	diazotize, add KI		236
2-Amino-5-nitropyridine	2-fluoro-5-nitropyridine	diazotize at 0° in 60% HF	22%	208
2-Amino-3-nitropyridine	2-chloro-3-nitropyridine	diazotize in HCl		233
2-Amino-5-nitropyridine	2-chloro-5-nitropyridine	diazotize in HCl		239
6-Amino-3-nitro-2-picoline	6-chloro-3-nitro-2-picoline, and 6-methyl-5-nitro-2-pyridinol	diazotize in HCl	29% and 49%	36

6-Amino-5-nitro-2-picoline	6-chloro-5-nitro-2-picoline, and 6-methyl-3-nitro-2-pyridinol	diazotize in conc. HCl with added $CaCl_2$, below 30°	38% and 30%	36
2-Amino-5-chloro-3-nitropyridine	2,5-dichloro-3-nitropyridine	diazotize in HCl		159
2-Amino-5-bromo-3-nitropyridine	5-bromo-2-chloro-3-nitropyridine	diazotize in HCl		159
6-Amino-5-bromo-3-nitro-2-picoline	5-bromo-6-chloro-3-nitro-2-picoline and 6-methyl-5-nitro-3-bromo-2-pyridinol	diazotize in HCl	32% and 27%	36
2-Amino-5-nitropyridine	2-iodo-5-nitropyridine	diazotize in HI	30–40%	99
		diazotize in HOAc with KI	14%	87
3-Aminopicolinic acid	3-chloropicolinic acid	Sandmeyer diazotization		38
3-Aminopicolinic acid	3-iodopicolinic acid	diazotize in acid, add KI		33
5-Aminonicotinic acid	5-chloronicotinic acid	Sandmeyer diazotization	18%	82
6-Aminonicotinic acid	6-chloronicotinic acid	treat with $NaNO_2$ and HCl in conc. H_2SO_4 solution		211
5-Aminonicotinic acid	5-bromonicotinic acid	Sandmeyer diazotization		39
5-Aminonicotinic acid	5-iodonicotinic acid	treat with $NaNO_2$ and KI in acid solution		39
Ethyl 5-aminonicotinate	ethyl 5-chloronicotinate	diazotize in HCl		37
3-Acetyl-5-aminopyridine	3-acetyl-5-fluoropyridine	diazotize in H_2SiF_6, then heat the diazonium salt in dry toluene	15%	168
5-Amino-2-chloro-6-methylnicotinonitrile	2,5-dichloro-6-methylnicotinonitrile	diazotize in HCl	27%	91
3-Amino-2-pyridinol	3-iodo-2-pyridinol	diazotize, treat with KI		236
5-Amino-2-pyridinol	5-iodo-2-pyridinol	diazotize, treat with KI		236
4-Aminopyridine 1-oxide	4-chloropyridine 1-oxide	Sandmeyer diazotization		171
4-Aminopyridine 1-oxide	4-bromopyridine 1-oxide	Sandmeyer diazotization		171

TABLE VI-11. Base Strength of the Monohalopyridines (*275*)

Compound	pK_a
Pyridine	5.17
2-Fluoropyridine	− 0.44
2-Chloropyridine	+ 0.72
2-Bromopyridine	0.90
2-Iodopyridine	1.82
3-Fluoropyridine	2.97
3-Chloropyridine	2.84
3-Bromopyridine	2.84
3-Iodopyridine	3.25

TABLE VI-12. Properties of the Halopyridines

Compound	Method of preparation	Physical properties, derivatives	Ref.
2-PyF	diazotization of 2-$PyNH_2$, and direct fluorination of PyH	b.p. 125°	204,203,115
3-PyF	diazotization of 3-$PyNH_2$	b.p. 106-8°/750 mm.	204,205,209
4-PyF	diazotization of 4-$PyNH_2$	b.p. 24-25°/20 mm. (impure); picrolonate, m.p. 195-97°	451
2-PyCl	from 1-methyl-2(1*H*)-pyridone with $POCl_3$, or pyridine 1-oxide with SO_2Cl_2	b.p. 168°; mercuric chloride, m.p. 177-78°	41,15
3-PyCl	diazotization of 3-$PyNH_2$, or thermal decomposition of Cl_2 addition compound	b.p. 148-49°; hydrochloride, m.p. 60°	209,57
4-PyCl	from 1-(4-pyridyl)pyridinium chloride with HCl, or diazotization of 4-$PyNH_2$	m.p. −42.5°; mercuric chloride, m.p. 250-60°; hydrochloride, m.p. 141.5-42.5°; picrate, m.p. 146°	138,186
2-PyBr	Craig diazotization of 2-$PyNH_2$, or by direct bromination of PyH at 500°	b.p. 193-94°/764 mm.; mercuric chloride, m.p. 184-85°; picrate, m.p. 105-6°	127,54,59
3-PyBr	direct bromination of PyH at 300°, or diazotization of 3-$PyNH_2$	b.p. 172-73°/752 mm.; mercuric chloride, m.p. 203°; picrate, m.p. 154°	53,209
4-PyBr	from 4-PyOH with PBr_5 or $POBr_3$, or by diazotization of 4-$PyNHNO_2$	m.p. 8.5-9.5°; b.p. 27.5-30°/0.4 mm.; picrate, m.p. 223°	138,142
2-PyI	diazotization of 2-$PyNH_2$	b.p. 93°/13 mm.	203,224
3-PyI	Gattermann diazotization of 3-$PyNH_2$ or iodination of PyH in oleum	m.p. 52-53°; picrate, m.p. 154°	209,219,95, 218

(*continued*)

TABLE VI-12. Properties of the Halopyridines (*continued*)

Compound	Method of preparation	Physical properties, derivatives	Ref.
4-PyI	from 4-PyCl with HI, or diazotization of 4-PyNH$_2$	m.p. 100°	135,218
2,3-Dichloropyridine	diazotization of 3-amino-2-chloropyridine	m.p. 66.5–67°; b.p. 202.5–3.5°	220
2,4-Dichloropyridine	diazotization of 2-amino-4-chloropyridine, or from 2,4-pyridinediol with POCl$_3$	m.p. −1 to 0°; b.p. 189–90°; hydrochloride, m.p. 76–77°	220
2,5-Dichloropyridine	from 1-methyl-2(1*H*)-pyridone with COCl$_2$, or diazotization of 2-amino-5-chloropyridine	m.p. 59–60°; mercuric chloride, m.p. 192–93°	140
2,6-Dichloropyridine	from 6-chloro-2-pyridinol with POCl$_3$	m.p. 85–87°	29,254,12
3,4-Dichloropyridine	Gattermann diazotization of 3-amino-4-chloropyridine	m.p. 23–23.5°; b.p. 182–83°	220
3,5-Dichloropyridine	direct chlorination of pyridine by thermal decomposition of the Cl$_2$ addition compound, and diazotization of 3-amino-5-chloropyridine	m.p. 67–68°; mercuric chloride, m.p. 183°	57,232,37, 187
2,3-Dibromopyridine	minor product in gas phase bromination of PyH at 300°	m.p. 58.5–59.5°; b.p. 249–49.5°; mercuric chloride, m.p. 176.5–77.5°	53
2,4-Dibromopyridine	from 2,4-pyridinediol with POBr$_3$	m.p. 38–38.5°; b.p. 237–37.5°; mercuric chloride, m.p. 161–62.5°	53
2,5-Dibromopyridine	from 2-amino-5-bromopyridine by diazotization, and as a minor product in the gas phase, bromination of pyridine at 300°	m.p. 93–94°; b.p. 238–38.5°; hydrochloride, m.p. 186–88°; mercuric chloride, m.p. 181–82°	53,216,229, 59
2,6-Dibromopyridine	gas phase bromination of 2-PyBr at 300°, or from 6-bromo-1-methyl-2(1*H*)-pyridone with POBr$_3$ · PBr$_5$	m.p. 118.5–19°; b.p. 255–55.5°	53,54,188

3,4-Dibromopyridine	a minor product in the gas phase bromination of pyridine	m.p. 71–72°; mercuric chloride, m.p. 113–14°	53
3,5-Dibromopyridine	one of two main products in the gas phase bromination of pyridine at 300°; from 3,5-bis-(chloromercuri)-pyridine with bromine and HBr	m.p. 111.5–12°; b.p. 227–27.5°; mercuric chloride, m.p. 207–8°	53,54,57, 258
2,5-Diiodopyridine	from 2-amino-5-iodopyridine by diazotization	m.p. 154°	88
2,6-Diiodopyridine	diazotization of 3-amino-2,6-diiodopyridine in ethanol	m.p. 183°	237
3,5-Diiodopyridine	a by-product in the direct iodination of pyridine, and from 1-pyridinesulfonic acid, ring opened, iodinated, ring closed	m.p. 173°; hydrochloride, m.p. 195–96°	97,95,244
2,3,4-Trichloropyridine	from 3-chloro-2,4-pyridinediol with $POCl_3$	m.p. 45–46°; b.p. 227–28°	220
2,3,5-Trichloropyridine	from 3,5-dichloro-1-methyl-2(1*H*)-pyridone with $COCl_2$ and by diazotization of 2-amino-3,5-dichloropyridine	m.p. 49–50°; b.p. 218–19°	140,189,34, 187
2,3,6-Trichloropyridine	from glutarimide with PCl_5	m.p. 66–67°	93
2,4,5-Trichloropyridine	from 4,5-dichloro-2-pyridinol or 5-chloro-2,4-pyridinediol with PCl_5, $POCl_3$, or Gattermann diazotization of 5-amino-2,4-dichloropyridine	m.p. 8–9°; b.p. 221.5–22.5°	26,220
2,4,6-Trichloropyridine	from 2-amino-4,6-dichloropyridine or 4-amino-2,6-dichloropyridine by diazotization	m.p. 33°	38,220
3,4,5-Trichloropyridine	from 3,5-dichloro-4-pyridinol with $POCl_3 \cdot PCl_5$	m.p. 76–77°	32

(continued)

TABLE VI-12. Properties of the Halopyridines *(continued)*

Compound	Method of preparation	Physical properties, derivatives	Ref.
2,3,4-Tribromopyridine	bromination of 3,4-dibromopyridine in the gas phase at 500°, or from 3-bromo-2,4-pyridinediol with $POBr_3$	m.p. 84–85°; mercuric chloride, m.p. 189–90.5°; b.p. 195.5–96°	31,53
2,3,5-Tribromopyridine	gas phase bromination of pyridine or 3,5-dibromopyridine	m.p. 45.5–46°; mercuric chloride, m.p. 183–85°; b.p. 286.5–87°	53,59
2,3,6-Tribromopyridine	gas phase bromination of 3-bromopyridine or 2,6-dibromopyridine	m.p. 83°	21
2,4,5-Tribromopyridine	gas phase bromination of 3,4-dibromopyridine or from 5-bromo-2,4-pyridinediol with $POBr_3$	m.p. 66.5–67.5°; mercuric chloride, m.p. 201–2°; b.p. 286–86.5°	53
2,4,6-Tribromopyridine	gas phase bromination of 4-bromo- or 2,6-dibromopyridine, or from 4-pyridinol with $POBr_3 \cdot PBr_5$ (as by-product)	m.p. 107–8°	142,21
3,4,5-Tribromopyridine	from 3,5-dibromo-4-pyridinol with $POBr_3$, or as a minor product in the gas phase bromination of pyridine at 300°	m.p. 106.5–7.5°; mercuric chloride, m.p. 201.5–2.5°; b.p. 284.5–85°	138,21,53,59
2,3,4,5-Tetrachloropyridine	direct halogenation of pyridine hydrochloride, from pyridine with PCl_5, or from 3,4,5-trichloro-2-pyridinol with PCl_5	m.p. 21–22°	12,10,268
2,3,4,6-Tetrachloropyridine	Gattermann diazotization of 3-amino-2,4,6-trichloropyridine	m.p. 37.5–38°; b.p. 248.5–49.5°	220
2,3,5,6-Tetrachloropyridine	from 3,5,6-trichloro-2-pyridinol with $POCl_3 \cdot PCl_5$	m.p. 90–91°	29

2,3,4,5-Tetrabromopyridine	gas phase bromination of 3,4,5-tribromopyridine, or from 2,4-pyridinediol with PBr_5-$POBr_3$	m.p. 74.5–75.5°	53
2,3,4,6-Tetrabromopyridine	bromination of several dibromopyridines	m.p. 105–6°; b.p. 334–34.5°	53,59
2,3,5,6-Tetrabromopyridine	from 3,5,6-tribromo-1-methyl-2(1*H*)-pyridone with PBr_5; or by diazotization of 2-amino-3,5,6-tribromopyridine	m.p. 104°	89,73
Pentachloropyridine	from pyridine by vigorous treatment with PCl_5, or by treatment of pyridine 1-oxide with sulfuryl chloride (by-product in each case)	m.p. 123–24°	15,10
Pentabromopyridine	gas phase bromination of 2-bromopyridine	m.p. 209.5–10°	59
Pentaiodopyridine	direct iodination of melted pyridine hydrochloride with iodine or ICl	m.p. 106°	97,95,57
Pentafluoropyridine	dehydrogenation of perfluoropiperidine	b.p. 84°	452
2-Bromo-5-chloropyridine	from 2-amino-5-chloropyridine by Craig diazotization	m.p. 70–71°	87
3-Bromo-2-chloropyridine	Gattermann diazotization of 3-amino-2-chloropyridine	m.p. 55.5–56.5°	19
3-Bromo-4-chloropyridine	from 3-bromopyridine 1-oxide with sulfuryl chloride (gives isomeric by-products)	m.p. 17.5–18.5°; picrate, m.p. 121.5–22.5°	19
5-Bromo-2-chloropyridine	by diazotization of 2-amino-5-bromopyridine; or from 5-bromo-1-methyl-2(1*H*)-pyridone with $COCl_2$	m.p. 71°	233,86,140, 19
2-Chloro-5-iodopyridine	from 5-amino-2-chloropyridine or 2-amino-5-iodopyridine by diazotization; or from 5-iodo-1-methyl-2(1*H*)-pyridone with $COCl_2$	m.p. 99°	236,101,140, 154,235

(*continued*)

TABLE VI-12. Properties of the Halopyridines *(continued)*

Compound	Method of preparation	Physical properties, derivatives	Ref.
2-Bromo-5-iodopyridine	from 2-amino-5-iodopyridine by diazotization	m.p. 122.5°	88
5-Bromo-2-iodopyridine	from 2-amino-5-bromopyridine by diazotization	m.p. 117°	88
5-Bromo-2,3-dichloropyridine	from 3-amino-5-bromo-2-chloropyridine by Gattermann diazotization	m.p. 30–31°	159
3-Bromo-2,4-dichloropyridine	from 3-bromo-2,4-pyridinediol with $POCl_3$	m.p. 55.5–56.5°	31
5-Bromo-2,4-dichloropyridine	from 5-bromo-2,4-pyridinediol with $POCl_3$	m.p. 21–22°	31
3,5-Dichloro-4-iodopyridine	from 3,4,5-trichloropicolinic acid with HI and red P.	m.p. 183°	33
2,4-Dibromo-3-chloropyridine	from 3-chloro-2,4-pyridinediol with $POBr_3$	m.p. 70–70.5°	220,53
2,4-Dibromo-5-chloropyridine	from 5-chloro-2,4-pyridinediol with $POBr_3$	m.p. 61.5–62.5°	26

3,5-Dibromo-2-chloropyridine	from 3,5-dibromo-1-methyl-2(1*H*)-pyridone or 3,5-dibromo-2-pyridinol with $COCl_2$ or $POCl_3$; or by diazotization of 2-amino-3,5-dibromopyridine	m.p. 43–44°	238,140,154
3,5-Dibromo-4-chloropyridine	from 3,5-dibromo-4-pyridinol with PCl_5	m.p. 98°	32
3,5-Dibromo-2-iodopyridine	from 2-amino-3,5-dibromopyridine by diazotization	m.p. 70.5°	88
2-Chloro-3,5-diiodopyridine	from 3,5-diiodo-1-methyl-2(1*H*)-pyridone with $COCl_2$ or PCl_5	m.p. 72–73°	99,140
4-Chloro-3,5-diiodopyridine	from 3,5-diiodo-4-pyridinol with PCl_5	m.p. 175°	32
3-Bromo-2,4,5-trichloropyridine	from 3-bromo-5-chloro-2,4-pyridinediol with $POCl_3$	m.p. 37–37.5°	26
5-Bromo-2,3,4-trichloropyridine	from 5-bromo-3-chloro-2,4-pyridinediol with $POCl_3$	m.p. 33.5–34°	31
2,3,4-Tribromo-5-chloropyridine	from 3-bromo-5-chloro-2,4-pyridinediol with $POBr_3$	m.p. 77.5–78.5°	26
2,4,5-Tribromo-3-chloropyridine	from 5-bromo-3-chloro-2,4-pyridinediol with $POBr_3$	m.p. 66.5–67.5°	31
2,4-Dibromo-3,5-dichloropyridine	from 3,5-dichloro-2,4-pyridinediol with $POBr_3$	m.p. 68.5–69°	440

TABLE VI-13. Properties of the Alkylhalopyridines

Compound	Method of preparation	Physical properties, derivatives	Ref.
2-Fluoro-3-picoline	from 2-amino-3-picoline by diazotization in HF	b.p. 144-46° /737 mm.	206
3-Fluoro-4-picoline	from 3-amino-4-picoline by Schiemann diazotization	b.p. 135-36° /748 mm.	210
5-Fluoro-3-picoline	from 5-amino-3-picoline by Schiemann diazotization	b.p. 139° /700 mm.; n_D^{25} 1.4788	168,169
2-Chloro-3-picoline	from 3-methyl-2-pyridinol with PCl_5	b.p. 192-93° /751 mm.	281
2-Chloro-4-picoline	from 4-methyl-2-pyridinol with PCl_5 ; or by diazotization of 2-amino-4-picoline	b.p. 194-95°	197,225
4-Chloro-2-picoline	by decarboxylation of 4-chloro-6-methylpicolinic acid	b.p. 162.5-63.5°	449
5-Chloro-2-picoline	from 5-amino-2-picoline by diazotization	m.p. 21° ; b.p. 164-65°	221,222
6-Chloro-2-picoline	from 6-amino-2-picoline by diazotization	b.p. 183.5-84°	223
2-Chloro-3-ethylpyridine	from 1-methyl-3-ethyl-2(1*H*)-pyridone with $POCl_3$	b.p. 208-9°	443
2-Chloro-4-propylpyridine	from 2-amino-4-propylpyridine by diazotization	b.p. 130-32° /30 mm.	227
6-Chloro-2-propylpyridine	from 6-propyl-2-pyridinol with $POCl_3$ and PCl_5	b.p. 81-82.5° /6 mm.	198
6-Chloro-2-isobutylpyridine	from 6-isobutyl-2-pyridinol with $POCl_3$ and PCl_5	b.p. 91-92° /9 mm.; n_D^{25} 1.5060	192
3-Chloro-2,6-lutidine	from 2,5-dimethylpyrrole with $CHCl_3$ and NaOEt	picrate, m.p. 150-51°; chloroplatinate, m.p. 212°	251,250
4-Chloro-2,6-lutidine	from 2,6-dimethyl-4-pyridinol or 2,6-lutidine 1-oxide or 4-nitro-2,6-lutidine 1-oxide with $POCl_3$ and PCl_5 ; or by diazotization of 4-amino-2,6-lutidine	b.p. 178° ; picrate, m.p. 166-67° ; nitrate, m.p. 207.5°	17,28, 104, 211
6-Chloro-2,3-lutidine	from 5,6-dimethyl-2-pyridinol with $POCl_3$-PCl_5	m.p. 10-11° ; b.p. 100-1° /18 mm.	195

6-Chloro-2,4-lutidine	from 4,6-dimethyl-2-pyridinol with $POCl_3$-PCl_5	m.p. 212–14°	196
4-Chloro-5-ethyl-2-picoline	from 4-amino-5-ethyl-2-picoline by diazotization	b.p. 38–39°/1 mm.; n_D^{25} 1.5170	213
6-Chloro-5-ethyl-2-picoline	from 6-amino-5-ethyl-2-picoline by diazotization	b.p. 205–9°; picrate, m.p. 139°; chloroplatinate, m.p. 190°	228
2-Chloro-3-ethyl-4-picoline	from 2,6-dichloro-3-ethyl-4-picoline with HI	b.p. 110°/12 mm.	201
6-Chloro-2-ethyl-4-picoline	from 6-ethyl-4-methyl-2-pyridinol with PCl_5	b.p. 224°/765 mm.	144
6-Chloro-2-*n*-butyl-3-picoline	from 6-*n*-butyl-5-methyl-2-pyridinol with PCl_5	b.p. 119.5–20.5°/8 mm.	193
6-Chloro-2,3,4-trimethylpyridine	from 4,5,6-trimethyl-2-pyridinol with PCl_5	m.p. 49°; b.p. 118–19°/20 mm. picrate, m.p. 105°	270
2-Chloro-6,7-dihydro-5*H*-1-pyrindine	from 6,7-dihydro-5*H*-1-pyrindine-2-ol with $POCl_3$-PCl_5	m.p. 70–71°	190
2-Chloro-6,7,8,9-tetrahydro-5-cyclohepta[b]pyridine	from 6,7,8,9-tetrahydro-5-cyclohepta[b]pyridin-2-ol with $POCl_3$-PCl_5	m.p. 69–69.5°	191
2-Chloro-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5-cyclopentadeca[b]pyridine	from 6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5-cyclopentadeca[b]pyridin-2-ol with $POCl_3$	b.p. 140–60°/0.1 mm.; picrate, m.p. 131°	170
5-Bromo-2-picoline	from 5-amino-2-picoline by Sandmeyer diazotization	m.p. 32°	222
6-Bromo-2-picoline	from 6-methyl-2-pyridinol with $POBr_3$; or from 6-amino-2-picoline by diazotization	b.p. 198–201°; picrate, m.p. 115–16°	92

(continued)

TABLE VI-13. Properties of the Alkylhalopyridines (*continued*)

Compound	Method of preparation	Physical properties, derivatives	Ref.
2-Bromo-3-picoline	Craig diazotization of 2-amino-3-picoline	b.p. 218–19°; 76–77°/7 mm.; n_D^{20} 1.5680	87
6-Bromo-3-picoline	Craig diazotization of 6-amino-3-picoline	m.p. 49–50°	87
2-Bromo-4-picoline	Craig diazotization of 2-amino-4-picoline	b.p. 223–24°	87
2-Bromo-4-ethylpyridine	diazotization of 2-amino-4-ethylpyridine	b.p. 103–105/11 mm.	230
2-Bromo-4-propylpyridine	from 2-amino-4-propylpyridine by diazotization	b.p. 133–35°/19 mm.	227
5-Iodo-2-picoline	diazotization of 5-amino-2-picoline, or by treating 2-picoline with iodine in oleum	m.p. 48–49°; b.p. 205–15°, 105–6°/18 mm.; picrate, m.p. 150°	96,222
3-Iodo-2-picoline	from 3-amino-2-picoline by diazotization	m.p. 36–37°; picrate, m.p. 168°	430
3-Iodo-4-picoline	from 4-picoline by iodination in fuming H_2SO_4	m.p. 160°	429
3-Iodo-2,4,6-trimethylpyridine	from 2,4,6-trimethylpyridine by iodination in fuming H_2SO_4	m.p. 102°	429
2,6-Dichloro-4-cyclopentylpyridine	from β-cyclopentylglutarimide with PCl_5	not purified	442
2,6-Dichloro-5-cyclopentyl-3-picoline	from α-cyclopentyl-α′-methyl-glutarimide with PCl_5	m.p. 54°	435
2,6-Dichloro-3,5-lutidine	from α, α′-dimethylglutarimide with PCl_5	m.p. 97–98°	93
2,4-Dichloro-3,6-lutidine	from 3,6-dimethyl-2,4-pyridinediol with PCl_5	b.p. 120°/12 mm.	200
2,4-Dichloro-6-ethyl-3-picoline	from 6-ethyl-3-methyl-2,4-pyridinediol with PCl_5	b.p. 125–30°/12 mm.	200

2,6-Dichloro-3-ethyl-4-picoline	from 3-ethyl-4-methyl-2,4-pyridinediol with $POCl_3$ or PCl_5	b.p. 140°/12 mm.	201
2,4-Dichloro-6,7-dihydro-5*H*-1-pyrindine	from 6,7-dihydro-5*H*-1-pyrindine-2,4-diol with $POCl_3$	b.p. 126–28°/11 mm.	146
1,3-Dichloro-6,7-dihydro-5*H*-2-pyrindine	from 6,7-dihydro-5*H*-2-pyrindine-1,3-diol with $POCl_3$	m.p. 36°	145
1,3-Dichloro-4-ethyl-6,7-dihydro-5*H*-2-pyrindine	from 4-ethyl-6,7-dihydro-5*H*-2-pyrindine-1,3-diol with $POCl_3$	b.p. 167–68°/11 mm.; m.p. 68°	145
2,4-Dichloro-5,6,7,8-tetrahydroquinoline	from 5,6,7,8-tetrahydroquinoline-2,4-diol with $POCl_3$-PCl_5	b.p. 149–50°/14 mm.	146
2,4,Dichloro-6,7,8,9-tetrahydro-5-cyclohepta[b]-pyridine	from 6,7,8,9-tetrahydro-5-cyclohepta[b]-pyridine-2,4-diol with $POCl_3$-PCl_5	oil	56
2,3,6-Trichloro-4-picoline	from β-methylglutarimide with PCl_5	m.p. 82–83°	434
2,5,6-Trichloro-3-picoline	from α-methylglutarimide with PCl_5	m.p. 94–95°	93
2,3,6-Trichloro-4-cyclopentylpyridine	from β-cyclopentylglutarimide with PCl_5	not purified	442
2,3,6-Trichloro-5-cyclopentylpyridine	from α-cyclopentylglutarimide with PCl_5	m.p. 141°	271
4-Bromo-5-ethyl-2-picoline	from 5-ethyl-4-nitro-2-picoline 1-oxide with PBr_3	b.p. 105–10°/20 mm.; picrate, m.p. 141–42°	255

(*continued*)

TABLE VI-13. Properties of the Alkylhalopyridines (*continued*)

Compound	Method of preparation	Physical properties, derivatives	Ref.
3-Bromo-2,6-lutidine	from 2,5-dimethylpyrrole with $CHBr_3$ and $NaOCH_3$	picrate, m.p. 148°	250
3,5-Dibromo-2,6-lutidine	bromination-decarboxylation of the potassium salt of 2,6-lutidine-3,5-dicarboxylic acid	m.p. 65°	263
3,5-Dibromo-*s*-collidine	bromination-decarboxylation of the potassium salt of *s*-collidine-3,5-dicarboxylic acid	m.p. 81°; b.p. 262–63/726 mm.; picrate, m.p. 159–60°	263
3,5,6-Tribromo-2-picoline	from 3,5-dibromo-6-methyl-2-pyridinol with $POBr_3$	m.p. 75–76°	92
3,4,5-Triiodo-2,6-lutidine	from 4-amino-3,5-diiodo-2,6-lutidine by diazotization, or by treating 4-chloro-3,5-diiodo-2,6-lutidine with HI	picrate, m.p. 221–23°	104
4-Chloro-3,5-diiodo-2,6-lutidine	from 4-amino-3,5-diiodo-2,6-lutidine by diazotization, and from 3,5-diiodo-2,-6-dimethyl-4-pyridinol with $POCl_3$	m.p. 148°	104
3,5-Diiodo-*s*-collidine	from *s*-collidine by iodination in fuming H_2SO_4	m.p. 20°; b.p. 122–23°/14 mm.	429
5-Chloro-3-*i*-propenylpyridine	from 5-chloro-α,α-dimethyl-3-pyridinemethanol by dehydration over alumina at 300°	b.p. 70–73°/3 mm.; n_D^{25} 1.5554	82
5-Bromo-3-vinylpyridine	from 5-bromo-α-methyl-3-pyridinemethanol by dehydration over alumina at 300°	b.p. 74–75°/3 mm.; n_D^{25} 1.5810	82
5-Bromo-3-*i*-propenylpyridine	from 5-bromo-α,α-dimethyl-3-pyridinemethanol by dehydration over alumina at 300° or with 20% H_2SO_4	b.p. 85–87°/3 mm.; n_D^{25} 1.5820	82

TABLE VI-14. Properties of the Arylhalopyridines

Compound	Method of preparation	Physical properties, derivatives	Ref.
4-Chloro-2-phenylpyridine	from 2-phenylpyridine 1-oxide with $POCl_3$ or SO_2Cl_2	picrate, m.p. 180–82°	272
6-Chloro-2-phenylpyridine	from 6-phenyl-2-pyridinol with PCl_5 or from 2-phenylpyridine 1-oxide with $POCl_3$ or SO_2Cl_2	m.p. 34°; b.p. 124–25°/0.1 mm.	272,147
4-Chloro-2,6-diphenylpyridine	from 1-methyl-2,6-diphenyl-4(1*H*)-pyridone or 2,6-diphenyl-4-pyridinol with $POCl_3$-PCl_5	m.p. 72°	273
2-Chloro-4,6-diphenylpyridine	from 4,6-diphenyl-2-pyridinol with $POCl_3$-PCl_5	m.p. 64–65°; b.p. 170–75°/0.25 mm.	438
2-Chloro-5-methyl-4,6-diphenylpyridine	from 5-methyl-4,6-diphenyl-2-pyridinol with $POCl_3$	m.p. 92–93°	202
2,6-Dichloro-3-phenylpyridine	from 3-phenyl-2,6-pyridinediol with $POCl_3$	m.p. 95–96°	40
2,6-Dichloro-3-(*p*-chlorophenyl)-pyridine	from 3-(*p*-chlorophenyl)-2,6-pyridinediol with $POCl_3$	m.p. 137–38°	40
2,4,5,6-Tetrachloro-3-phenylpyridine	from 3-phenyl-2,6-pyridinediol with $POCl_3$	m.p. 101–3°	40
2-Bromo-4-phenylpyridine	Craig diazotization of 2-amino-4-phenylpyridine	m.p. 65–66°	230
6-Bromo-2-phenylpyridine	Craig diazotization of 6-amino-2-phenylpyridine	m.p. 51–52°	230

TABLE VI-15. Properties of the Haloalkylhalopyridines

Compound	Method of preparation	Physical properties, derivatives	Ref.
5-Chloro-2-(trifluoromethyl)pyridine	by treatment of 5-chloro-2-(trichloromethyl)pyridine with HF	m.p. 37.5–38°; b.p. 151–52°/744.6 mm.	8
3,5-Dichloro-2-(trifluoromethyl)pyridine	from 3,5-dichloro-2-(trichloromethyl)-pyridine with HF	m.p. 15°; b.p. 177–78°/747.4 mm.	8
4-Chloro-2-(trichloromethyl)pyridine	from picolinic acid with PCl_5, and also from 4,5-dihydroxypicolinic acid with $POCl_3$-PCl_5	not well described	7
5-Chloro-2-(trichloromethyl)pyridine	direct chlorination of 2-picoline in water	m.p. 45.5–46.5°; b.p. 139–42°/25 mm.	8
3,5-Dichloro-2-(trichloromethyl)pyridine	direct chlorination of 2-picoline in water	m.p. 35.5–36.5°; b.p. 161–62/25 mm.	8
4,5-Dichloro-2-(trichloromethyl)pyridine	from 4,5-dihydroxypicolinic acid with PCl_5 and also from picolinic acid with PCl_5	not well described	265 7
4,6-Dichloro-3-(2-chloroethyl)-2-picoline	from 5-(2-ethoxyethyl)-6-methyl-2,4-pyridinediol with $POCl_3$	m.p. 55–56°	148
2,6-Dichloro-3-(2-chloroethyl)-4-picoline	from 2,3-dihydro-4-methylfuro[2,3-b]-pyridin-6-ol with $POCl_3$	m.p. 68.9°	143

3,4,5-Trichloro-2-(trichloromethyl)pyridine	direct chlorination of 2-picoline in water	m.p. 99–100°; b.p. 172–75°/25 mm.	8
4,5,6-Trichloro-2-(trichloromethyl)pyridine	from 4,5-dihydroxypicolinic acid with PCl_5	not well characterized	265
2-(Bromomethyl)-4-chloropyridine	bromination of 4-chloro-2-picoline with NBS (*N*-bromosuccinimide)	hydrobromide, m.p. 173° (dec.)	433
2-(Dibromomethyl)-4-chloropyridine	bromination of 4-chloro-2-picoline with NBS	m.p. 73–75°	433
6-(Bromomethyl)-4-chloro-2-picoline	bromination of 4-chloro-2,6-lutidine with NBS	hydrobromide, m.p. 225°	433
6-(Dibromomethyl)-4-chloro-2-picoline	bromination of 4-chloro-2,6-lutidine with NBS	m.p. 81–82°	433
6-(Tribromomethyl)-4-chloro-2-picoline	bromination of 4-chloro-2,6-lutidine with NBS	m.p. 126–28°	433
2,6-Bis(chloromethyl)-4-chloropyridine	from 4-chloro-2,6-pyridinedimethanol with $SOCl_2$	m.p. 55–56.5°	433
3-Chloro-2,6-bis(trifluoromethyl)pyridine	treatment of the corresponding trichloromethylpyridine with HF	m.p. 1.6–2.0°; b.p. 164–65°/748 mm.	437
3-Chloro-2,6-bis(trichloromethyl)pyridine	chlorination of 2,6-bis(trichloromethyl)pyridine	m.p. 86.5–87.5°; b.p. 180–85°/9 mm.	437

TABLE VI-16. Compounds of Polyvalent Iodine

Compound	Melting point, °C.	Ref.
3-Iodopyridine dichloride	128–30	209,279
2-Chloro-5-iodopyridine dichloride	115	282
	107	279,280,283
2-Amino-5-iodopyridine dichloride	133	280
2-Methoxy-5-iodopyridine dichloride	119	280
2-Acetamino-5-iodopyridine dichloride	220 (dec.)	280
2-Chloro-5-iodosopyridine	200–5 (dec.)	279,280
2-Acetamino-5-iodosopyridine	155	280
2-Chloro-5-iodoxypyridine	205 (dec.)	282

TABLE VI-17. Side-Chain Halopyridines from Hydroxyalkylpyridines and Related Starting Materials

Starting material	Compound	Reagent	Physical properties, derivatives	Ref.
2-$PyCH_2NH_2$	2-$PyCH_2Cl$	$NaNO_2$ in HCl	b.p. 73–76° /10 mm.; picrate, m.p. 152–53°	158,190
3-$PyCH_2OH$	3-$PyCH_2Cl$	$SOCl_2$	m.p. 142–45°	338
4-$PyCH_2OH$	4-$PyCH_2Cl$	$SOCl_2$	m.p. 170–75°	338
2-$PyCH_2CH_2OH$	2-$PyCH_2CH_2Cl$	$SOCl_2$	m.p. about 120°	374
4-$PyCH_2CH_2OH$	4-$PyCH_2CH_2Cl$	HCl	hydrochloride, m.p. > 260°; picrate, m.p. 130–31°; chloroplatinate, m.p. 147–48°	276
4-$PyCH_2CH_2I$	4-$PyCH_2CH_2Cl$	AgCl + HCl		390
6-Methyl-2-pyridinemethanol	6-(chloromethyl)-2-picoline	PCl_3	picrate, m.p. 162–63°	431
2,5-Dimethyl-3-pyridinemethanol	3-(chloromethyl)-2,5-lutidine	$SOCl_2$	m.p. 30°	432
2,6-Dimethyl-3-pyridinemethanol	3-(chloromethyl)-2,6-lutidine	$SOCl_2$	m.p. 45–56°	432
4,6-Dimethyl-3-pyridinemethanol	5-(chloromethyl)-2,4-lutidine	$SOCl_2$	m.p. 151–52°	432
4,5,6-Trimethyl-3-pyridinemethanol	5-(chloromethyl)-2,3,4-trimethylpyridine	PCl_5	m.p. 66°	441
2,6-Dimethyl-3,4-pyridinedimethanol	3,4-bis(chloromethyl)-2,6-lutidine	$SOCl_2$	liquid	441
2,6-Dimethyl-3,5-pyridinedimethanol	3,5-bis(chloromethyl)-2,6-lutidine	$SOCl_2$	m.p. 107°	441
3-PyCHOHMe	3-PyCHClMe	$SOCl_2$	hydrochloride, m.p. 111–12°	365,375
3-Acetopyridine	3-(1-chlorovinyl)-pyridine	PCl_5	b.p. 112–14°/24 mm.	392
3-Methyl-α-propyl-2-pyridinemethanol	2-(1-chlorobutyl)-3-picoline	$SOCl_2$	reaction intermediate	354

(continued)

TABLE VI-17. Side-Chain Halopyridines from Hydroxyalkylpyridines (*continued*)

Starting material	Compound	Reagent	Physical properties, derivatives	Ref.
5-Methyl-α-propyl-2-pyridinemethanol	6-(1-chlorobutyl)-3-picoline	$SOCl_2$	reaction intermediate	354
3-Methyl-α-phenyl-2-pyridinemethanol	2-(α-chlorobenzyl)-3-picoline	$SOCl_2$	reaction intermediate	66
α,6-Diphenyl-3-pyridinemethanol	5-(α-chlorobenzyl)-2-phenylpyridine	PCl_5	m.p. 79°	377
3,4-Bis(aminomethyl)-pyridine	3,4-bis(chloromethyl)-pyridine	$NaNO_2$ in HCl		396
3-(2-Ethoxyethyl)-2-picoline	3-(2-chloroethyl)-2-picoline	HCl	picrate, m.p. 134–35°	149
2-PyCHEtCH$_2$OH	2-PyCHEtCH$_2$Cl	HCl	(unstable)	378
2-PyCH$_2$OH	2-PyCH$_2$Br	HBr in HOAc	hydrobromide, m.p. 146°	366
4-PyCH$_2$OH	4-PyCH$_2$Br	HBr in HOAc 49% aq. HBr	hydrobromide, m.p. 149–50°	366 379
6-Methyl-2-pyridine-ethanol	6-(2-bromoethyl)-2-picoline	HBr	picrate, m.p. 111°	380,381
2-PyCH$_2$CH$_2$CH$_2$OH	2-PyCH$_2$CH$_2$CH$_2$Br	HBr in HOAc	m.p. 104–7°	444
4-PyCH$_2$CH$_2$CH$_2$OMe	4-PyCH$_2$CH$_2$CH$_2$Br	HBr	hydrobromide hygroscopic	439
2-PyCH$_2$CHOHMe	2-PyCH$_2$CHBrMe	HBr	picrate, m.p. 105°	382
2-PyCH$_2$CHOHEt	2-PyCH$_2$CHBrEt	HBr + red P	picrate, m.p. 143–44°	378
2-Py(CH$_2$)$_{11}$OEt	2-Py(CH$_2$)$_{11}$Br	HBr	hydrobromide, m.p. 94.5°	383
o-NO$_2$C$_6$H$_4$CHOHCH$_2$-Py-2	*o*-NO$_2$C$_6$H$_4$CHBrCH$_2$Py-2	HBr in HOAc	hydrobromide, m.p. 220°	384
2,6-Pyridinedimethanol	2,6-bis(bromomethyl)pyridine	HBr in H_2SO_4	m.p. 66–77°	385

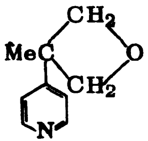
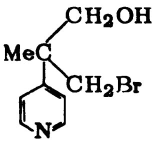
		HBr in HOAc	m.p. 180-81°	386
2-PyCMe(CH$_2$OH)$_2$	2-PyCMe(CH$_2$Br)CH$_2$OH	HBr in HOAC	hydrobromide, m.p. 180–81°	386
3-Hydroxy-2-pyridinemethanol	2-bromomethyl-3-pyridinol	HBr	hydrobromide, m.p. 187–88°	367
3-Hydroxy-6-methyl-2-pyridinemethanol	2-bromomethyl-6-methyl-3-pyridinol	HBr	hydrobromide, m.p. 224°	367,387
3-Hydroxy-2,6-pyridinedimethanol	2,6-bis(bromomethyl)-3-pyridinol	HBr	hydrobromide, m.p. 188–90°	367
3-Methoxy-2-methyl-4,5-pyridinedimethanol	4,5-bis(bromomethyl)-2-methyl-3-pyridinol	HBr	hydrobromide, m.p. 217°	262,388 389
3-Amino-5-(aminomethyl)-4-(ethoxymethyl)-2-picoline	3-Amino-5-(aminomethyl)-4-(bromomethyl)-2-picoline	HBr		175
2-PyCH$_2$CH$_2$OH	2-PyCH$_2$CH$_2$I	HI + red P	chloroplatinate, m.p. 149–50°; picrate, m.p. 111–12°	371
4-PyCH$_2$CH$_2$OH	4-PyCH$_2$CH$_2$I	HI + red P	picrate, m.p. 114–15°; hydroiodide, m.p. 186–87°	276,390
2-PyCH$_2$CHOHMe	2-PyCH$_2$CHIMe	HI + red P	· 1/2 chloroplatinate, m.p. 152–53°	371
2-PyCH(CH$_3$)CH$_2$OH	2-PyCH(CH$_3$)CH$_2$I	HI	picrate, m.p. 87–89°; · 1/2 chloroplatinate, m.p. 142–45°	370,372
2-PyCH$_2$CHOHEt	2-PyCH$_2$CHIEt	HI	chloroplatinate, m.p. 136–39°	378
3-PyCHOHPr	3-PyCHIPr	HI + red P		448
2-PyCMe(CH$_2$OH)$_2$	2-PyCMe(CH$_2$OH)CH$_2$I	HI		372
4-PyC(CH$_2$OH)$_3$	4-PyC(CH$_2$I)$_3$	HI + red P	m.p. 136°	373

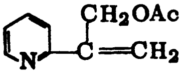
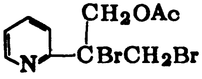
TABLE VI-18. Halostilbazoles and Related Compounds

Starting material	Compound	Reagent	Physical properties, derivatives	Ref.
2-Stilbazole	2-PyCHClCHClC_6H_5	Cl_2 in CCl_4	m.p. 153–54°	397
2,6-Distyrylpyridine	6-(α,β-dichlorophenethyl)-2-stilbazole	Cl_2	m.p. 213°	398
2'-Nitro-2-stilbazole	2-(α,β-dichloro-*o*-nitrophenethyl)pyridine	Cl_2 in CCl_4	m.p. 176° (dec.); picrate, m.p. 167–68° (dec.)	399
2-Vinylpyridine with *p*-chlorobenzenediazonium chloride	*p*-Cl$C_6H_4CH_2$CHClPy-2		b.p. 150–58°/1 mm.	234
2-Stilbazole	2-PyCHBrCHBrPh	Br_2 in CCl_4	m.p. 172°	397,398
4-Stilbazole	α-(or β-)bromo-4-stilbazole	Br_2, then HOAc, reflux	hydrochloride, m.p. 189–90°	364
2,2'-Vinylenedipyridine	2-PyCHBrCHBrPy-2	Br_2	m.p. 153–54°	400
4'-Methyl-2-stilbazole	*p*-MeC_6H_4CHBrCHBrPy-2	Br_2 in CS_2	hydrobromide, m.p. 170° (dec.)	401
4'-*i*-Propyl-2-stilbazole	2-(α,β-dibromo-*p*-*i*-propylphenethyl)pyridine	Br_2 in CS_2	m.p. 159–60°	402
2'-Hydroxy-2-stilbazole	*o*-HOC_6H_4CHBrCHBrPy-2	Br_2 in dil. HCl		403
6-Methyl-2-stilbazole	6-(α,β-dibromophenethyl)-2-picoline	Br_2 in CCl_4	m.p. 178°	405

4′,6-Dimethyl-2-stilbazole	6-(α,β-dibromo-*p*-methylphenethyl)-2-picoline	Br_2 in CS_2	m.p. 154°	406
4,6-Dimethyl-2-stilbazole	6-(α,β-dibromophenethyl)-2,4-lutidine	Br_2		407
2′-Nitro-2-stilbazole	*o*-$NO_2C_6H_4CHBrCHBrPy$-2	Br_2 in CCl_4	m.p. 182°	384,399
4-Methyl-4′-nitro-2-stilbazole	2-(*p*-nitro-α,β-dibromophenethyl)-4-picoline	Br_2		404
4′-Amino-4-methyl-2-stilbazole	2-(*p*-amino-α,β-dibromophenethyl)-4-picoline	Br_2	m.p. 157° (dec.)	404
2′-Nitro-6-phenyl-2-stilbazole	2-(α,β-dibromo-*o*-nitrophenethyl)-6-phenylpyridine	Br_2 in CS_2	m.p. 145°	408
5-Ethyl-3′-nitro-2-stilbazole	2-(α,β-dibromo-*m*-nitrophenethyl)-5-ethylpyridine	Br_2		409
2,6-Distyrylpyridine	2,6-bis(α,β-dibromophenethyl)pyridine and 6-(α,β-dibromophenethyl)-2-stilbazole	Br_2	m.p. 214–15°	398
2,6-Bis(*p*-methylstyryl)pyridine	2,6-bis(α,β-dibromo-*p*-methylphenethyl)pyridine	Br_2	m.p. 182°	406
2,6-Bis(*p*-nitrostyryl)pyridine	2,6-bis(α,β-dibromo-*p*-nitrophenethyl)pyridine	Br_2	m.p. 252°	406
o-Nitrostyryl 2-pyridyl ketone	a tetrabromo derivative	Br_2	m.p. 120°	411
6-(α,β-Dibromophenethyl)-2,4-lutidine	6-(α-bromostyryl)-2,4-lutidine	elimination of HBr	m.p. 213–14°	407

TABLE VI-19. Other Side-Chain Halopyridines

Starting material	Compound	Reagent	Physical properties, derivatives	Ref.
F_3CCN with butadiene	2-trifluoromethylpyridine		b.p. 142–44°	339
2,4-Bis(trichloromethyl)pyridine	2,4-bis(trifluoromethyl)pyridine	HF	b.p. 126–27°/746 mm.	8
2,6-Bis(trichloromethyl)pyridine	2,6-bis(trifluoromethyl)pyridine	HF	b.p. 149–50°/748 mm.; m.p. 56.5–57.5°	8
2-Picoline	2-trichloromethylpyridine	Cl_2 in HOAc with KOAc, or Cl_2 in H_2O	m.p. – 10°; b.p. 112–15°/15 mm., 125–26°/25 mm.; acetate, m.p. 127°	8,360
4-Picoline	4-trichloromethylpyridine	Cl_2 in H_2O	b.p. 105–7°/18 mm.	447
2-Trichloromethylpyridine	2-dichloromethylpyridine	$SnCl_2$ in acetone	b.p. 90–92°/15–16 mm.	360,422
4-Trichloromethylpyridine	4-dichloromethylpyridine	Sn + HCl in acetone	B.p. 78–80°/18 mm.	447
2,6-Dichloro-3-(2-chloroethyl)-4-picoline	3-(2-chloroethyl)-4-picoline	H_2 over Pd-C in HCl	hydrochloride, m.p. 170–71°	143
2,4-Lutidine	2,4-bis(trichloromethyl)pyridine	Cl_2	m.p. 86.5–87.5°	8

2,6-Lutidine	2,6-bis(trichloromethyl)pyridine	Cl_2 in H_2O	m.p. 83.5-84.5°	8
		HCl with $SOCl_2$	m.p. 86–87° : b.p. 165–67°/12 mm.	359
s-Collidine	2,4,6-tris(trichloromethyl)-pyridine	Cl_2 in H_2O	m.p. 166–68°	8
2-Picoline	2-(bromomethyl)pyridine	NBS with benzoyl peroxide	picrate, m.p. 152–53°	433
3-Picoline	3-bromomethylpyridine	Br_2 in HCl	picrate, m.p. 114°	333,361
5-Ethyl-2-picoline	5-(1-bromoethyl)-2-picoline	Br_2	m.p. 154°	362
2-Picoline	2-(dibromomethyl)pyridine	NBS with benzoyl peroxide	picrate, m.p. 144–45°	433
2-Pyridineacrylic acid	α,β-dibromo-2-pyridinepropionic acid	Br_2 in HOAc	m.p. 127°	393,410
2-Pyridineacrylic acid	β-bromo-2-pyridinepropionic acid	HBr	m.p. 163–64°	393
4-Pyridineacrylic acid	α,β-dibromo-4-pyridinepropionic acid	Br_2	m.p. 258-60°	392
		Br_2	m.p. 89–90°	412

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CHAPTER VII

Organometallic Compounds of Pyridine

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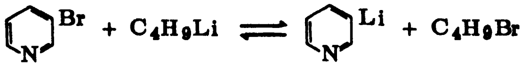
The synthesis and reactions of pyridine derivatives in which a metal atom is linked directly, or by a carbon chain, to the pyridine nucleus will be discussed in this chapter. Since phosphorus, arsenic, and antimony compounds of pyridine are discussed in Chapter XVI, this chapter will include the other known organometallic compounds of pyridine, namely, the lithium, sodium, potassium, magnesium, mercury, thallium, tin, lead, and silicon compounds.

A. LITHIUM COMPOUNDS

1. Preparation

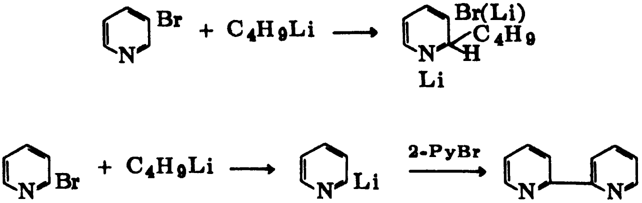
a. By Halogen-Metal Interconversion

Nuclear halogenated pyridine derivatives do not react satisfactorily with metallic lithium to form pyridyllithium compounds (*5*). Gilman and Spatz (*72,73,147,148*), however, found that 2-bromopyridine, 3-bromopyridine, or 3-iodopyridine reacted with an alkyllithium compound like *n*-butyllithium at –35 to 0° to give good yields of the corresponding pyridyllithium compound (VII-1). The



(VII-1)

metal-halogen interconversion reaction, carried out in either diethyl ether or petroleum ether as solvent, was rapid even at these low temperatures and achieved equilibrium essentially within 15–30 minutes. The combination of low temperature and short reaction time kept to a minimum a number of competing reactions such as addition to the azomethine linkage or coupling to form dipyridyl derivatives (VII-2).



(VII-2)

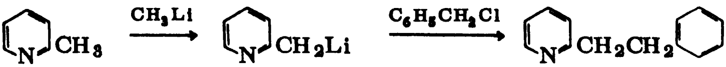
Gilman and Spatz (*73*) found that 3,5-dibromopyridine or 2,6-dibromopyridine and *n*-butyllithium led to the formation of 3-bromo-5-pyridyllithium and 2-bromo-6-pyridyllithium, respectively. There was no evidence of di-interconversion even when a large excess of *n*-butyllithium was used and the reaction period was extended.

Recently, Wibaut and Heeringa (*193*) reported the successful preparation of 4-pyridyllithium by the reaction of 4-bromopyridine and *n*-butyllithium at –75°; 4-chloropyridine did not react with either lithium metal or *n*-butyllithium.

b. By Lateral Metalation

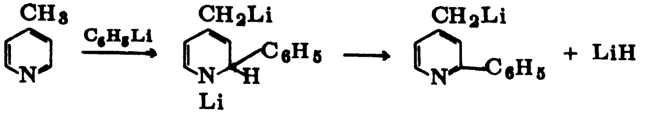
The term metalation is used for the replacement of hydrogen by a metal to form a new carbon-metal linkage.

(a) With Methyllithium. Ziegler and Zeiser (*189*) were the first to employ an organolithium compound for the metalation of 2-picoline. With an ethereal solution of methyllithium they obtained 2-picolyllithium; reaction of 2-picolyllithium with benzyl chloride gave 2-phenethylpyridine (VII-3). 3,5-Lutidine and methyllithium, however, gave 2,3,5-collidine (*199*).



(VII-3)

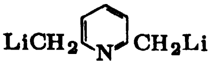
(b) With Phenyllithium. Bergmann and Rosenthal (*17*) found that phenyllithium and methylpyridines in diethyl ether gave picolyllithium derivatives. Prijs, Lutz, and Erlenmeyer (*129*) reported that 4-picoline and phenyllithium in refluxing diethyl ether gave a product in which metalation and addition to the azomethine linkage had occurred (VII-4). By slowly adding an ether solution of



(VII-4)

phenyllithium to an ether solution of 4-picoline, Wibaut and Hey (*171*) circumvented the addition to the azomethine linkage and obtained good yields of 4-picolyllithium. There are no reports of the reaction of 3-picoline with phenyllithium.

The metalation product from one mole each of 2,6-lutidine and phenyllithium was 2-methyl-6-picolyllithium (*32,77,92,97*); however, the nature of the metalation product from one mole of 2,6-lutidine and two moles of phenyllithium is uncertain. Bergmann and Rosenthal (*17*) and Bergmann and Pinchas (*18*) assigned structure VII-5 to the reaction product. More recent and detailed work by de Jong and Wibaut (*92*) and Kloppenburg and Wibaut (*97*) makes doubtful the existence of VII-5. The reactions of this metalation product

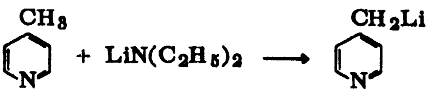


(VII-5)

will be discussed in a later section of this chapter (p. 430). 2,4-Lutidine and phenyllithium gave a mixture of 4-methyl-2-picolyllithium and 2-methyl-4-picolyllithium (*4,57*).

An important reaction was also described by Gruber and Schlögl (*79*), who obtained 5-nitro-2-picolyllithium by the reaction of 5-nitro-2-picoline with phenyllithium. Normally, the nitro group undergoes complex reactions with the reactive organometallic compounds (*22*), and this is apparently the first successful preparation of a reactive organometallic compound containing a nitro group.

(c) **With Lithium Diethylamide.** Wibaut and Hey (*171*) prepared 4-picolyllithium by the reaction of 4-picoline with lithium diethylamide (VII-6). While no experimental details were presented, it



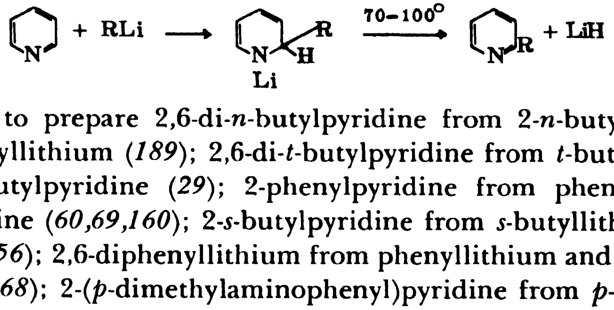
(VII-6)

was stated that this method of preparation gave yields of 4-picolyllithium comparable to those obtained from 4-picoline and phenyllithium. It is of interest to note that lithium diethylamide does not add to the azomethine linkage as does sodium amide (see p. 435).

(d) With Lithium Amide. Bergstrom (*19*) reported that 2-picoline reacted with lithium amide to give low yields of 2-picolyllithium.

c. By Addition to the Azomethine Linkage

While studying the conductivity of organosodium and organopotassium compounds in solution in various solvents, Ziegler and his co-workers (*187–189*) observed, on adding these compounds to pyridine, that a deep red color formed promptly. Since attempts to ascertain the structure of these red-colored complexes were unsuccessful, they chose to study the effects of alkyl- and aryllithium compounds on pyridine. On employing molar ratios of 1:1 and heating the solutions to 70–100°, the formation of a precipitate was observed. They were able to show that the precipitate was lithium hydride and deduced correctly that they had found a new method for the synthesis of 2-alkyl- and 2-arylpyridines (VII-7). This method



(VII-7)

was used to prepare 2,6-di-*n*-butylpyridine from 2-*n*-butylpyridine and *n*-butyllithium (*189*); 2,6-di-*t*-butylpyridine from *t*-butyllithium and 2-*t*-butylpyridine (*29*); 2-phenylpyridine from phenyllithium and pyridine (*60,69,160*); 2-*s*-butylpyridine from *s*-butyllithium and pyridine (*56*); 2,6-diphenyllithium from phenyllithium and 2-phenylpyridine (*68*); 2-(*p*-dimethylaminophenyl)pyridine from *p*-dimethylaminophenyllithium and pyridine (*68*); 2-(*p*-dimethylaminophenyl)-6-(*p*-tolyl)pyridine from 2-(*p*-dimethylaminophenyl)pyridine and *p*-tolyllithium (*68*); and 2-butylpyridine from *n*-butyllithium and pyridine (*182*). The only reported failure of this synthetic method was that 2-*s*-butylpyridine and phenyllithium did not react (*56*). The synthesis of alkylpyridines (p. 171) and arylpyridines (p. 217) by this reaction is discussed in Chapter V.

2. Properties

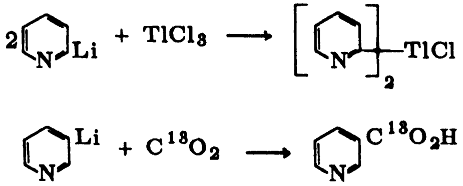
The pyridyllithium and picolyllithium compounds have been prepared only in solution in anhydrous solvents like diethyl ether and petroleum ether, as intermediates for further synthesis. Since there are no reports of their isolation from these solutions, no information is available on their physical properties. The pyridyllithium compounds, being thermally unstable, are best prepared at –40 to –30° and employed synthetically at temperatures below 0°. The picolyllithium compounds are more stable thermally and have been used in reactions at 75–80°.

Grunwald (*80*) has reported that 2-picolyllithium gave characteristic absorption in the infrared with several maxima and minima.

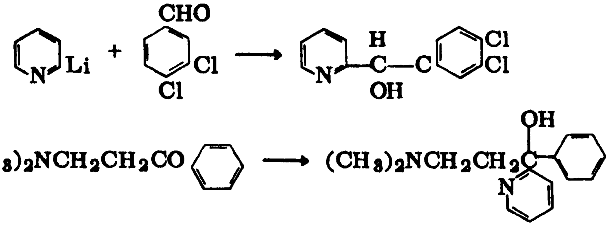
3. Reactions

a. Pyridyllithium Compounds

The reactions of pyridyllithium compounds are typical of the highly reactive organometallic compounds. Thus, 2-pyridyllithium and thallium trichloride gave bis(2-pyridyl)thallium chloride (*1*), while the reaction of 3-pyridyllithium with $C^{13}O_2$ or $C^{14}O_2$ led to the synthesis of C^{13}- or C^{14}-labeled nicotinic acid (VII-8). (*Cf.* Chapter X.) Sperber *et al.* (*150*) found that 2-pyridyllithium and various aromatic aldehydes gave 70–90% yields of carbinols; such yields were far superior to those obtained from 2-pyridylmagnesium bromide and the same aldehydes (*149*). In similar fashion, Adamson and Billinghurst (*2,3*) prepared a series of carbinols in 33–83% yield by the reaction of 2- and 3-pyridyllithium with various dialkylaminoalkyl aryl ketones (VII-9). In this study it was reported that the re-

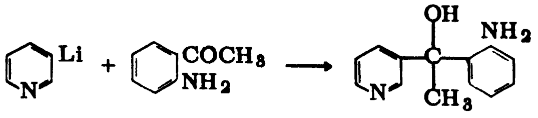


(VII-8)



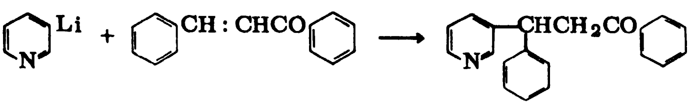
(VII-9)

action of 2-pyridylmagnesium bromide with the same ketones was unsuccessful (*3,155*). Nunn and Schofield (*117,136*) reacted a number of alkyl aminophenyl ketones with two or three equivalents of either 2- or 3-pyridyllithium and obtained 50–80% yields of carbinols (VII-10). The single exception to this general method for the



(VII-10)

synthesis of tertiary carbinols was the reaction between benzalacetophenone and 3-pyridyllithium, which gave as the only identifiable product the 1,4-addition compound (VII-11) in 10% yield.

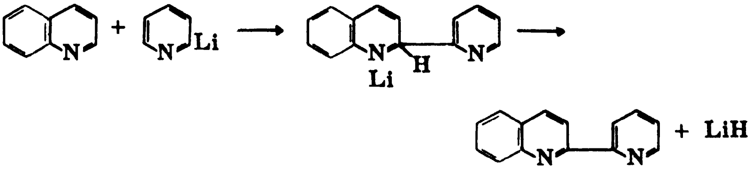


(VII-11)

The reactions of 2- and 3-pyridyllithium with esters were of interest also, since by using equivalent amounts of ester and lithium compound it was possible to obtain either a ketone or a mixture of ketone and tertiary carbinol; as expected when the molar ratio was 1:2, only tertiary carbinol was formed (*174*). Wibaut and de Jonge (*174*) have reported the isolation of α-phenyl-2-pyridinemethanol from the reaction of ethyl benzoate and 2-pyridyllithium. This product was presumed to arise via reduction of phenyl 2-pyridyl ketone by 2-pyridyllithium and is apparently the first report of reduction by an organolithium compound. The preparation of carbinols is also discussed in Chapter XIII.

Nitriles reacted normally with 2- and 3-pyridyllithium to give 40–60% yields of ketones (*63,70,174*).

2-Pyridyllithium added to the azomethine linkage of quinoline at −20° to give 2-(2-pyridyl)quinoline in 33% yield (VII-12) (*70*).

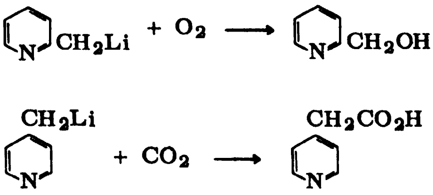


(VII-12)

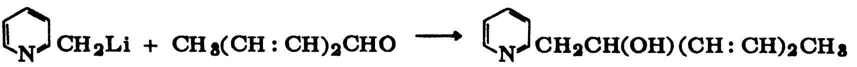
The reactions of 2-, 3-, and 4-pyridyllithium are listed in Tables VII-1 to VII-4 (pp. 445 ff.).

b. Picolyllithium Compounds

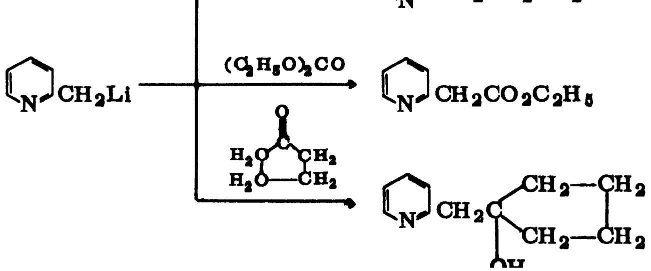
The reactions of the picolyllithium compounds have been thoroughly explored. With oxygen, 2-picolyllithium gave 2-pyridinemethanol (*59*), while with carbon dioxide, 2- and 4-picolyllithium gave the corresponding pyridineacetic acids (VII-13) (*25,56,79,84,169,185*). When treated with bromine, 2-picolyllithium yielded 1,2-bis(2-pyridyl)ethane (*37*). With aldehydes, 2-picolyllithium gave the expected carbinols; it was of interest that crotonaldehyde and sorbaldehyde were reported to give only 1,2-addition products (VII-14) (*4,57*). With 2-picolyllithium, ethylene oxide yielded 2-pyridinepropanol (*74,116*); a variety of ketones gave tertiary carbinols (*42,74,117,136,138*); and ethyl carbonate gave ethyl 2-pyridineacetate (VII-15) (*78*). β-Ionone was reported to give only the 1,2-addition product (VII-16) (*4,57*).



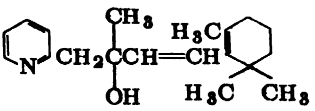
(VII-13)



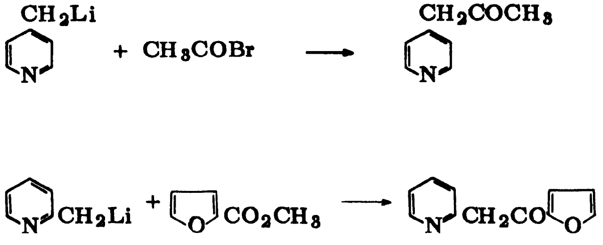
(VII-14)

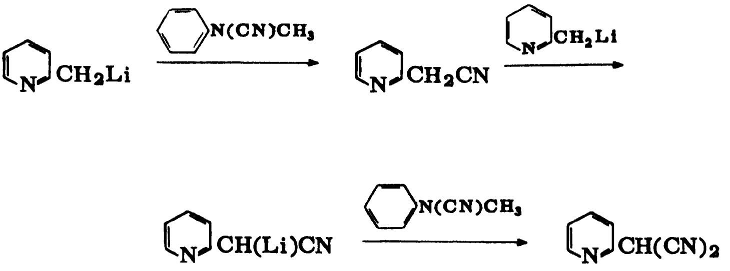


(VII-15)


(VII-16)

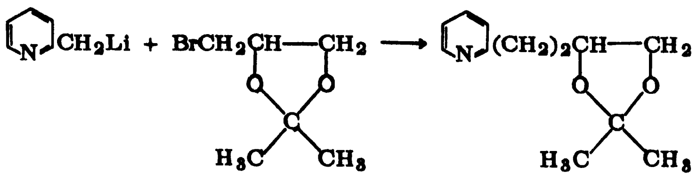
The reactions of acyl halides or esters of aromatic or heterocyclic acids with 2-picolyllithium are apparently unique in giving only ketones (VII-17) (*77,84,169*). While esters of the aliphatic acids generally gave mixtures of ketone and tertiary carbinol (*12,13,76,77*), ethyl ethoxyacetate was reported to yield only ethoxymethyl 2-pyridyl ketone (*180*). Ketones are also produced by the reaction of 2-picolyllithium with nitriles (*32,92,173*). An interesting reaction has been reported by Lettré *et al.* (*105*), who found that 2-picolyllithium and *N*-cyano-*N*-methylaniline gave 2-pyridylmalononitrile; the proposed mechanism is shown (VII-18).


(VII-17)

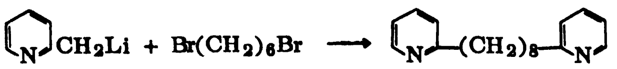

(VII-18)

4-Picolyllithium and esters of aliphatic, aromatic, or heterocyclic acids have yielded a number of new ketones (*206*).

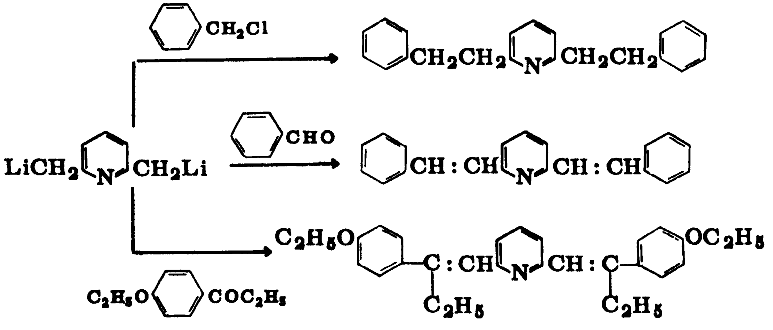
The reaction of 2- and 4-picolyllithium with brominated acetals and ketals, alkyl bromides, and alkylene bromides has led to a large number of new alkylated pyridines (VII-19) (*11,53,54,85,90,171*)



(VII-19)

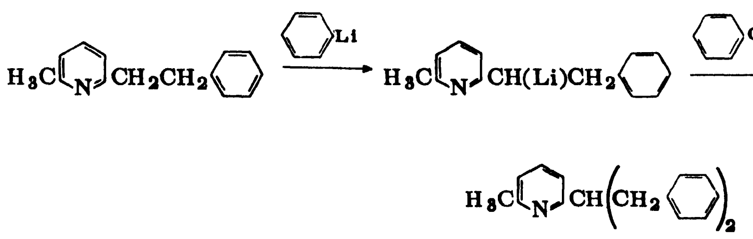


In studying the metalation product from 2,6-lutidine and phenyllithium, and its reactions with benzyl chloride or ethyl bromide, Bergmann and Rosenthal (*17*) and Bergmann and Pinchas (*18*) reported the isolation of products which they assumed to be 2,6-diphenethylpyridine and 2,6-dipropylpyridine, respectively. In order to explain the formation of these products as well as those presumed to be formed by the reaction of the metalation product with benzaldehyde and 4-ethoxypropiophenone, these authors postulated the formation of a dilithium derivative (VII-20).

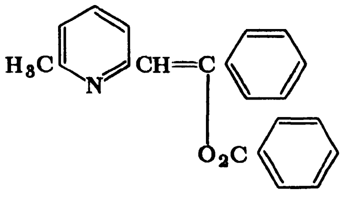


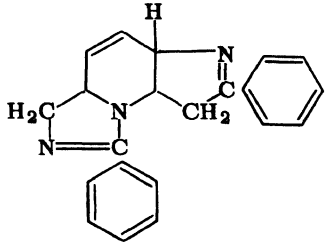
(VII-20)

De Jong and Wibaut (*92*) reinvestigated the reactions of 2,6-lutidine with phenyllithium, but did not confirm the above findings. With a molar ratio of 1:1, the product was, in fact, 6-methyl-2-picolyllithium, since on reaction with benzyl chloride, 6-methyl-2-phenethylpyridine was obtained. When a molar ratio of 1:2 was used, reaction with benzyl chloride gave 6-methyl-2-phenethylpyridine, 2-(dibenzylmethyl)-6-methylpyridine and a trace amount of 3(or 4 or 5)-benzyl-6-methyl-2-phenethylpyridine. In addition, the same authors showed that the reaction of 6-methyl-2-phenethylpyridine first with phenyllithium and then with benzyl chloride also gave 2-(dibenzylmethyl)-6-methylpyridine (VII-21).


(VII-21)

De Jong and Wibaut further reported (*92*) that the metalation product from 2,6-lutidine and phenyllithium (molar ratio 1:2) reacted with benzoic anhydride to give VII-22 and with benzonitrile to give what is suggested to be VII-23. Goldberg and Levine (*194*) obtained VII-22 from the reaction of 2,6-lutidine and phenyllithium (0.2 mole each) followed, in sequence, by 0.1 mole each of methyl benzoate and benzoyl chloride.


(VII-22)

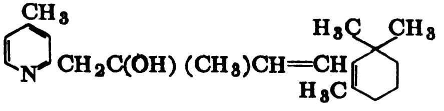

(VII-23)

Some evidence for the dilithium derivative was found in the report of Barnes and Fales (*197*) that the bromination of the reaction product from 2,6-lutidine and phenyllithium gave a 1% yield of 2,6-di(bromomethyl)pyridine and large amounts of a polymeric material.

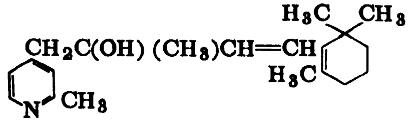
2-Methyl-6-picolyllithium has proved useful in other syntheses. With benzonitrile, it gave 2-(6-methyl-2-pyridyl)acetophenone (*92*) and with esters of aliphatic, aromatic, and heterocyclic acids, 50–

95% yields of 6-methyl-2-picolyl ketones. With the esters of aliphatic acids some tertiary carbinol was also formed (*77*).

2,4-Lutidine and phenyllithium gave a mixture of 4-methyl-2-picolyllithium and 2-methyl-4-picolyllithium, since on reaction with β-ionone, two isomeric carbinols (VII-24 and VII-25) were obtained (*4,57*).



(VII-24)



(VII-25)

The reaction of tetraacetyl-α-D-glucosyl bromide with 2-picolyllithium gave a complex mixture of products; only 2-pyridyl-2-propanone and 1,3-bis(2-pyridyl)-2-methyl-2-propanol were identified (*88*).

While 2-ethyl- and 2-*i*-butylpyridines are readily metalated by either methyllithium or phenyllithium, 2-*i*-propyl- and 2-*s*-butylpyridines are not (*56,203*). 3-Picoline and phenyllithium gave 6-phenyl-3-picoline (*204*).

The reactions of 2-picolyllithium are listed in Tables VII-5 to VII-8 (pp. 448 ff.); those of substitution products of 2-picolyllithium in Table VII-9 (pp. 452 ff.). Reactions of 4-picolyllithium are listed in Table VII-10 (p. 455).

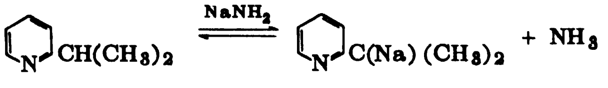
B. SODIUM COMPOUNDS

1. Preparation

The known organosodium compounds of pyridine are limited to the side-chain derivatives; they have always been prepared by metalation with sodium amide. This reaction was first reported by Chichibabin and his co-workers (*39,44*). Metalation occurred readily when a 2- or 4-methyl- or -ethylpyridine was ground with sodium amide at room temperature. Under these conditions, it was reported that the 3-ethyl group did not react.

Bergstrom (*19*) reported that 2-picoline, 2,4-lutidine, and *sym*-collidine reacted sluggishly and incompletely with sodium amide in liquid ammonia to give low yields of organosodium compounds. These observations remained largely unchallenged until Brown and Murphey (*30*) undertook a detailed study of the reaction. They found that the addition of 2-, 3-, or 4-picoline to a suspension of sodium amide in liquid ammonia caused the instantaneous development of an intense color, indicating rapid conversion to the corresponding picolylsodium derivative. In several instances, these intensely colored solutions could be titrated with methyl chloride to a sharp end-point in a matter of minutes to give 51–66% yields of the ethylpyridine. With compounds like 2-ethyl- or 2-*i*-propylpyridine, conversion to the sodium derivative was significantly slower, so that it was necessary to react these compounds with sodium amide at 75–80° in order to obtain 30–60% yields of 2-*i*-propyl- and 2-*t*-butylpyridines, respectively.

That the metalation of alkylpyridines by sodium amide is an equilibrium reaction can be shown by the reaction of 2-*i*-propylpyridine (VII-26) with sodium amide. When methyl chloride was passed into the reaction mixture fairly rapidly (35 minutes) the color was discharged and a 7% conversion to 2-*t*-butylpyridine obtained; when the methyl chloride was added slowly (eight hours) at a rate which did not eliminate the intense color, the conversion was 60%. The low conversion during the rapid addition was due to the preferential reaction of the methyl chloride with sodium amide (methylamine was a by-product of these reactions), rather than with the small concentration of the picolylsodium derivative present (VII-27).



(VII-27)

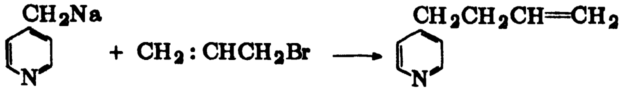
(VII-26)

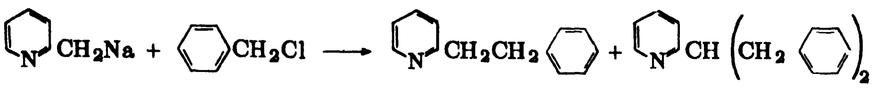
2. Properties

Since the picolylsodium derivatives are highly reactive organometallic compounds, they have generally been prepared in liquid ammonia and utilized *in situ;* in this solvent they form intensely colored solutions. In a few instances these compounds have undergone reaction at 75–80°, indicating considerable thermal stability. Pyridylsodium compounds are not known.

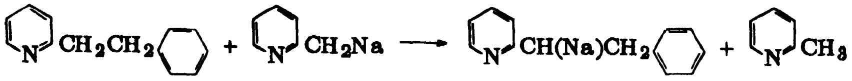
3. Reactions

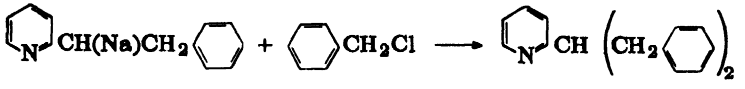
2-Picolylsodium reacted with acetic anhydride or acetonitrile to give 2-pyridyl-2-propanone (*134*). 2-, 3-, and 4-Picolylsodium with alkyl and aralkyl chlorides, bromides, or iodides generally gave good yields of the higher alkyl- and aralkylpyridines. In most instances, the reaction was simple and led to the one expected derivative; however, with methyl chloride, methyl iodide, and benzyl chloride, a secondary reaction occurred to give, in addition, a small amount of a dialkylated product (VII-28). The dialkylated product can arise, of course, by metalation of the monoalkylated pyridine by either sodamide or the picolylsodium. The later would give rise to the "exchange reaction" of Brown and Murphey (*30*) (VII-29). As shown by Bergstrom, Norton, and Seibert (*22*), the exchange reaction may be minimized by the rapid addition of the reacting halide to the picolylsodium derivative.





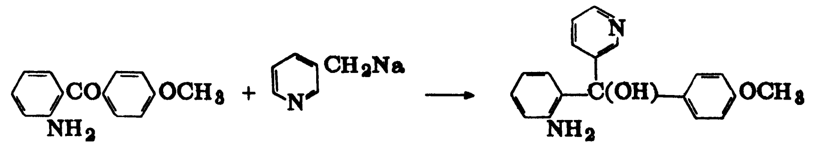
(VII-28)



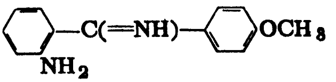


(VII-29)

2- and 3-Picolylsodium reacted normally with 2-amino-4'-meth oxybenzophenone to give the expected carbinol (VII-30); it was first presumed that 4-picolylsodium reacted anomalously with the ketone since only the ketimine (VII-31) was obtained. It was subsequently



(VII-30)



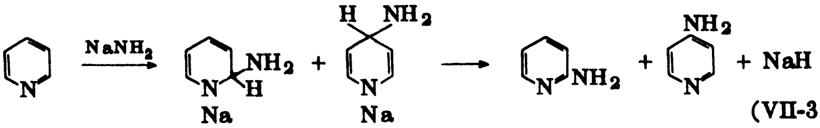
(VII-31)

shown that VII-31 was formed when the ketone was treated only with sodium amide in liquid ammonia, so that 4-picolylsodium did not react, apparently, with the ketone. The formation of ketimines from ketones and sodium amide in liquid ammonia had not been previously reported (*118*).

The reactions of 2-picolylsodium are listed in Table VII-11, 3-picolylsodium in Table VII-12, and 4-picolylsodium in Table VII-13 (pp. 455 ff.).

4. Reaction of Sodium Amide with the Azomethine Linkage

At low temperatures, sodium amide metalates the picolines to give picolylsodium derivatives. At elevated temperatures, *i.e.*, 130–200°, sodium amide adds selectively across the azomethine linkage. This method is used commercially to prepare aminopyridines and aminopicolines. The principal product arises as a result of 1,2-addition, but smaller amounts of 1,4-addition also occur (VII-32). (*Cf.* Chapter IX.)

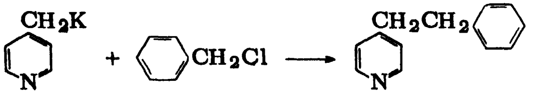


(VII-32)

C. POTASSIUM COMPOUNDS

1. Preparation

Like the sodium compounds, organopotassium compounds of pyridine are limited to side-chain derivatives and are prepared by metalation with the alkali metal amide. Potassium amide was first used by Bergstrom (*19*) as a metalating agent for the methylpyridines. He reasoned that potassium amide was more soluble than sodium amide in liquid ammonia and might consequently be a better metalating agent. In his earlier investigations Bergstrom was generally unsuccessful; some years later, however, Bergstrom, Norton, and Seibert (*22*) described the successful preparation and aralkylation of 2- and 4-picolylpotassium in liquid ammonia. By this procedure they prepared a series of 2- and 4-aralkylpyridines in 56–99% yield (VII-33). The introduction of a second or third aralkyl group was minimized by the rapid addition of the aralkyl halide. Aralkylation failed when the aralkyl halide had an ortho nitro group or an "active" hydrogen.

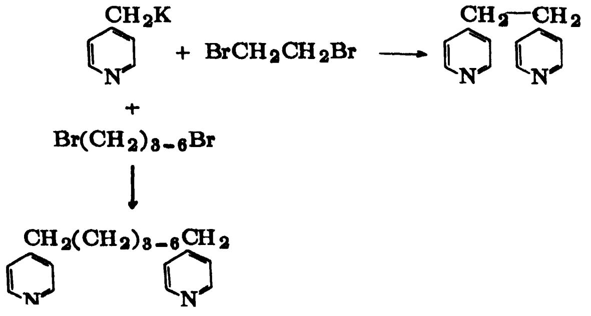

(VII-33)

2. Properties

The properties of the picolylpotassium derivatives are similar to those of the picolylsodium derivatives. Pyridylpotassium compounds, like pyridylsodium compounds, are unknown.

3. Reactions

The reactions described for 2- and 4-picolylpotassium were similar to those of the picolylsodium compounds. The single anomalous reaction reported was that between 4-picolylpotassium and 1,2-dibromoethane, which gave only 1,2-bis(4-pyridyl)ethane instead of the expected 1,4-bis(4-pyridyl)butane; the 1,3-, 1,4-, 1,5-, and 1,6-dibromoalkanes reacted normally (VII-34) (*90*).


(VII-34)

The reactions of 2-, 3-, and 4-picolylpotassium are listed in Tables VII-14, VII-15, and VII-16, respectively (pp. 458 f.).

D. GRIGNARD COMPOUNDS

1. Preparation

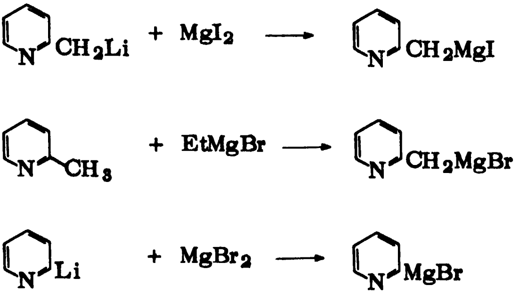
The earliest attempt to form a Grignard compound from a "bromopyridine" and magnesium was reported briefly by Sachs and Sachs (*190*). Many years later, Harris (*81*) found that 3-bromopyridine and 3,5-dibromopyridine in diethyl ether did not react with magnesium in the cold. At higher temperatures, tars were formed, but the reaction mixture gave a positive color test for the Grignard reagent with Michler's ketone. 2-Iodopyridine and magnesium also gave tars. Den Hertog and Wibaut (*83*) later reported unsuccessful attempts to form Grignard compounds from 2-bromo- and 2-iodopyridines; small amounts of 2,2′-dipyridyl were isolated. Overhoff and Proost (*120*) found that 2-bromopyridine and magnesium did not react in diethyl ether to any appreciable extent; with undiluted 2-bromopyridine, however, magnesium reacted exothermically and gave a tar, from which 2,2′-dipyridyl was also isolated.

In view of these unpromising observations on the direct methods for preparing magnesium compounds of pyridine, Overhoff and Proost (*120*) sought other approaches. The method which was successful was the entrainment procedure of Grignard (*191*). In this technique, the reaction is initiated between magnesium and a small amount of ethyl bromide in diethyl ether, and is subsequently maintained by the addition of a mixture of 2-bromopyridine and ethyl bromide. The continuous addition of ethyl bromide and the formation of ethylmagnesium bromide, by maintaining a clean magnesium surface, apparently makes possible the continuous formation of 2-pyridylmagnesium bromide, in spite of the separation of the Grignard compound as an oil which soon solidifies (*155*). In the absence of ethyl bromide, the 2-pyridylmagnesium bromide, as it separates, coats all of the magnesium and soon stops the reaction. By adding benzaldehyde to a mixture of Grignard reagents prepared by the entrainment procedure, it was possible to obtain α-phenyl-2-pyridinemethanol in 40–55% yields.

A second procedure used by Overhoff and Proost was to initiate the reaction by adding to the magnesium under diethyl ether a few drops of methyl iodide along with several drops of the reaction mixture obtained by adding aluminum powder to ethylene bromide. Now it was possible to add 2-bromopyridine in the usual manner and maintain the reaction. However, addition of benzaldehyde to such a Grignard mixture gave α-phenyl-2-pyridinemethanol in only 10–16% yields, indicating poorer yields of 2-pyridylmagnesium bromide by this procedure.

The entrainment procedure was applied by Overhoff and Proost to 3-pyridylmagnesium bromide and by others to 2-pyridylmagnesium iodide (*74*), 3-methyl-2-pyridylmagnesium bromide (*99*), 4-methyl-2-pyridylmagnesium bromide (*99*), 6-methyl-2-pyridylmagnesium bromide, (*131*), and 4-pyridylmagnesium chloride (*82,193*). Tetrahydrofuran has also been used as the solvent for these reactions (*99*).

Gilman and Towle (*74*) prepared 2-picolylmagnesium bromide and iodide by the metal-metal interconversion of 2-picolyllithium with magnesium bromide or magnesium iodide. Profft and Schneider (*196*) found that 2-picoline and ethylmagnesium bromide in refluxing tetrahydrofuran, dipropyl ether, or dibutyl ether gave 2-picolylmagnesium bromide. Gilman, Gregory, and Spatz (*70*) prepared 2-pyridylmagnesium bromide from 2-pyridyllithium and magnesium bromide (VII-35).

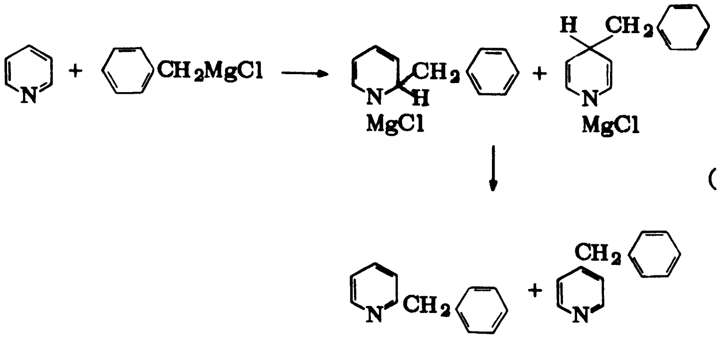


(VII-35)

2. Reactions

The pyridylmagnesium halides are typical Grignard compounds and similar in their reactions to the pyridyllithium derivatives. They react with aldehydes to give secondary carbinols, with ketones to give tertiary carbinols, with ethyl orthoformate to give acetals, with acid halides and esters to give mixtures of ketone and tertiary carbinol, with acid anhydrides and nitriles to give ketones, and with alkyl halides to give alkylated pyridines. It would appear that in several of these reactions the Grignard compound gives poorer yields than the corresponding lithium derivative (*149,150*).

The alkylation of pyridines by addition of the Grignard reagent across the azomethine linkage has also been described. Thus, Bergmann and Rosenthal (*17*) reported that pyridine and dibenzylmagnesium gave 2-benzylpyridine, while Veer and Goldschmidt (*156*) found that pyridine and benzylmagnesium chloride gave 4-benzylpyridine. Benkeser and Holton (*15*) resolved these differences by a series of careful experiments which showed that pyridine and benzylmagnesium chloride gave an 8% yield of product which was 20% 2-benzylpyridine and 80% 4-benzylpyridine (VII-36). The report by Bergstrom and McAllister (*21*) that pyridine and phenylmagnesium bromide or ethylmagnesium bromide at 150–160° gave 2-phenylpyridine and 2-ethylpyridine, respectively, was apparently in error, at least with respect to the latter product, since on repeating the experiment, Goetz-Luthy (*75*) obtained only dipyridyls. Doering and Pasternak (*56*) reported that pyridine and *s*-butylmagnesium bromide at 150–160° gave a 6% yield of 2-(*s*-butyl)pyridine and a 4% yield of 4-(*s*-butyl)pyridine.



(VII-36)

This reaction is further discussed in Chapter V (p. 171). The reactions of pyridylmagnesium and picolylmagnesium halides are listed in Tables VII-17 and VII-18 (pp. 460 f.).

E. MERCURY COMPOUNDS

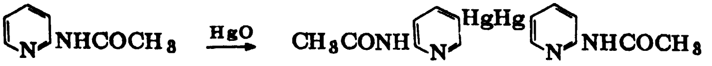
1. Preparation

a. Via Nuclear Substitution

The monomercuration in yields as high as 50% of pyridine (*89, 109,121,122,135,140–142,153*), 2-picoline (*153*), 4-picoline (*50*), 2-pyridinol (*6,26*), and 2-aminopyridine (*162*) by means of mercuric acetate has been reported. The ease of mercuration can be correlated with the electron-releasing effects of the substituents in the pyridine ring (*153*). Orientation follows the usual pattern: pyridine gave 3-pyridylmercuric acetate; 2-picoline gave 2-methyl-5-pyridylmercuric acetate; 4-picoline gave 4-methyl-3-pyridylmercuric acetate; 2-pyridinol gave 2-hydroxy-5-pyridylmercuric acetate; and 2-aminopyridine gave 2-amino-5-pyridylmercuric acetate and 2-amino-3-pyridylmercuric acetate. In several instances, the acetate was not isolated as such, but was converted to the more insoluble mercuric halide derivative by treatment, in solution, with aqueous sodium chloride, bromide, or iodide.

Di- and polymercurations were avoided by carrying out the reactions in the presence of small amounts of water in sealed tubes or autoclaves (*153*).

There is also an unconfirmed report (*123*) of the mercuration of 2-acetamidopyridine by mercuric oxide (VII-37).



(VII-37)

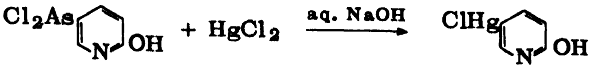
b. Via a Diazonium Compound

Nesmeyanov and Lutsenko (*113*) obtained 3-pyridylmercuric chloride, bromide, and iodide by the reaction of 3-pyridinediazonium chloride with mercuric chloride, mercuric bromide, and mercuric iodide, respectively. Decomposition of the 3-pyridinediazonium chloride–mercuric chloride complex by copper bronze in acetone, however, gave bis(3-pyridyl)mercury (*195*).

c. Via Metal-Metal Interconversion

2-Pyridyllithium and mercuric chloride in ether were reported by Gilman, Gregory, and Spatz (*70*) to give bis(2-pyridyl)mercury.

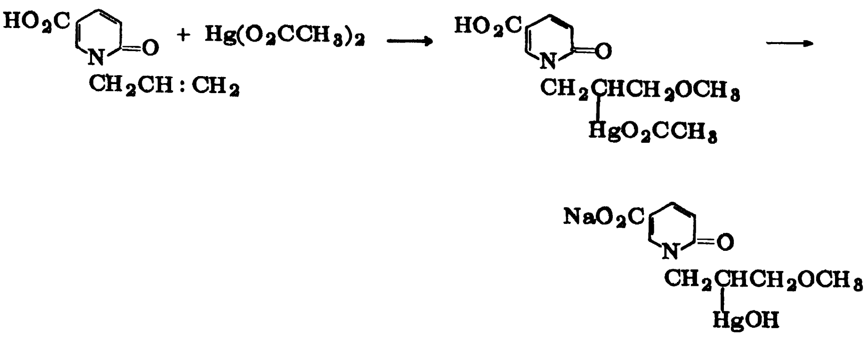
Binz, Räth, and Maier-Bode (*6*) obtained 2-hydroxy-5-pyridylmercuric chloride from dichloro(2-hydroxy-5-pyridyl)arsine, aqueous sodium hydroxide, and mercuric chloride (VII-38).



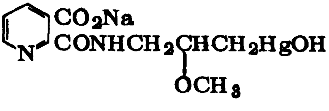
(VII-38)

d. Via Addition to a Carbon-Carbon Double Bond

1-Allyl-2(1*H*)-pyridone-5-carboxylic acid and mercuric acetate gave 1-(2-acetoxymercuri-3-methoxypropyl)-2(1*H*)-pyridone-5-carboxylic acid, which was converted by aqueous sodium hydroxide into sodium 1-(2-hydroxymercuri-3-methoxypropyl)-2(1*H*)-pyridone-5-carboxylate (VII-39), *36,87*). Werner and Scholz (*164*) used this procedure to obtain VII-40.



(VII-39)



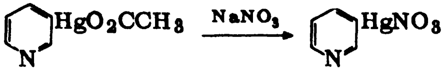
(VII-40)

2. Properties

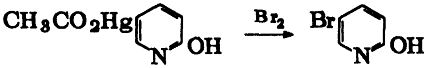
The mercury compounds of pyridine are obtained as crystalline, relatively high melting solids, and are very stable toward hydrolytic or other cleavage reactions of the carbon-mercury bond. They are not precipitated by proteins (*153*).

3. Reactions

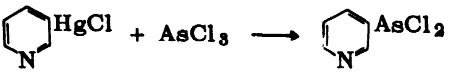
The pyridylmercuric acetates undergo double decomposition reactions with aqueous solutions of sodium chloride, bromine, iodide,


(VII-41)

and nitrate (VII-41). With the halogens, the nuclear mercury atom is replaced (VII-42); this reaction is useful for determining the position of ring mercuration (*153*). An exception was reported by Clemo and Swan (*50*), who found that 4-methyl-3-pyridylmercuric acetate did not react with bromine. 3-Pyridylmercuric acetate and aqueous sodium thiosulfate gave an 85% yield of bis(3-pyridyl)mercury; 3-pyridylmercuric hydroxide and copper bronze in water yielded a trace of bis(3-pyridyl)mercury; 2-pyridinesulfinic acid and mercuric chloride gave 2-pyridylmercuric chloride; and 6-chloro-3-pyridinesulfonyl chloride and mercuric chloride gave 6-chloro-3-pyridylmercuric chloride (*195*).


(VII-42)

McClelland and Wilson (*110*) obtained dichloro-3-pyridylarsine from 3-pyridylmercuric chloride and arsenic trichloride (VII-43).


(VII-43)

4. Applications

3-Pyridylmercuric chloride, acetate, stearate, and nitrate have been recommended as fungicides and bactericides for glues, varnishes, rubber, and gelatines (*8,9,23,24,35,86,104,108,130,140–143, 152,153,161*). 3-Pyridylmercuric acetate has been patented for use in mothproofing (*58*). It has proved effective as a prophylactic against bacterial gill disease in salmon (*34*), but is too toxic for use with trout (*62,132,133,184*). 3-Pyridylmercuric acetate and chloride have been used as termite repellents (*157,183*), and to protect sugar cane cuttings from the pineapple disease organism (*81*). Compounds of the type represented by VII-39 and VII-40 have been recommended as diuretics.

Sowa (*146*) has solubilized 3-pyridylmercuric acetate in water by the addition of ammonium salts, *e.g.,* ammonium sulfate.

The known mercury derivatives of pyridine are listed in Table VII-19 (pp. 462 f.).

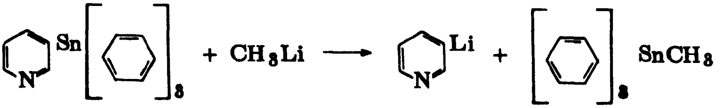
F. THALLIUM COMPOUNDS

2-Pyridyllithium and thallium chloride gave bis(2-pyridyl)thallium chloride, m.p. 288–290°, in 80% yield (*1*). With silver lactate in pyridine, bis(2-pyridyl)thallium chloride gave bis(2-pyridyl)thallium lactate, m.p. 205–208° (dec.). The complex $TlCl_3 \cdot (C_5H_5N)_3$ heated ten hours at 180° gave no pyridylthallium compound.

The pyridylthallium compounds were stable, insoluble in water, and more soluble in pyridine.

G. TIN COMPOUNDS

3-Pyridyllithium and triphenyltin chloride, at –35°, gave 3-pyridyltriphenyltin, m.p. 220°; 3-pyridyltriphenyltin formed a methiodide, m.p. 183–184°. 2-Pyridyltriphenyltin, similarly prepared, m.p. 178–179°, reacted with methyl iodide to give an intractable product. When 3-pyridyltriphenyltin was treated with methyllithium, no addition across the azomethine linkage occurred; instead metal-metal interconversion took place, presumably as shown (VII-44). Apparently, the carbon-tin linkage at the 3 position in the pyridine ring contributes to the deactivation of the azomethine linkage toward addition of the methyllithium.



(VII-44)

An attempt to prepare a 2-pyridyltin compound by refluxing metallic tin with 2-bromopyridine was unsuccessful (*71*).

2-Picolyllithium (from 2-picoline and butyllithium) and triethyltin chloride gave 2-picolyltriethyltin, b.p. 120–121°/3–4 mm. A similar reaction starting with 4-picoline gave a mixture of products: 2-*n*-butyl-4-picoline, hexaethyldistannane and (2-*n*-butyl-4-picolyl)-triethyltin, b.p. 144–145°/3–4 mm. 2-Picolyltriethyltin is readily hydrolyzed by moist air to give triethyltin hydroxide (*202*).

H. LEAD COMPOUNDS

Gilman, Gregory, and Spatz (*70*) treated diphenyllead diiodide with 2-pyridylmagnesium bromide at −15° and obtained a 63% yield of diphenyl-2-pyridyllead iodide, m.p. 137–140°. Diphenyl-2-pyridyllead iodide and phenylmagnesium bromide gave a 67% yield of 2-pyridyltriphenyllead, m.p. 220° (dec.).

An unresolved mixture of organolead compounds was obtained from the reaction between 2-pyridyllithium and diphenyllead diiodide. Triphenyllead iodide did not react with 2-pyridylmagnesium bromide. There was no evidence of metal-metal interconversion between 2-pyridyltriphenyllead and butyllithium or between tetraphenyllead and 2-pyridyllithium at −50°.

I. SILICON COMPOUNDS

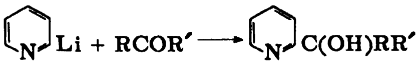
By first adding chlorotrimethylsilane to magnesium metal in dry pyridine, then adding 2-chloropyridine in pyridine, and refluxing the mixture, 2-pyridyltrimethylsilane was obtained, b.p. 88–90°/38 mm. The same compound was obtained from a mixture of ethyl bromide, magnesium, chlorotrimethylsilane, iodine, and 2-bromopyridine. The compound is useful as an additive to silicone oils; its salts are emulsifying and ion-exchange agents (*28*).

2-Picolylpotassium and chlorotrimethylsilane in liquid ammonia gave a 6.7% yield of 2-picolyltrimethylsilane, b.p. 191–192° (picrate, m.p. 124°) and a 13.3% yield of 2-[bis(trimethylsilyl)methyl]pyridine, b.p. 237.0–237.5° (this compound gave no picrate). 4-Picolylpotassium and chlorotrimethylsilane under the same conditions gave only a 10.3% yield of 4-picolyltrimethylsilane, b.p. 73–74°/4.5 mm. (picrate, m.p. 120°). When the above two picrates were refluxed in ethanol only the picrates of 2-picoline and 4-picoline, respectively, were recovered, indicating the lability of the C-Si bond in these compounds. It was noteworthy that 2- and 4-picolyltrimethylsilanes were readily cleaved by refluxing with aqueous alcohol; under these conditions, 2-[bis(trimethylsilyl)methyl]pyridine was unaffected; however, all three silanes were decomposed by dilute aqueous-alcoholic potassium hydroxide or dilute aqueous hydrochloride acid (*192*).

The reaction of 2-benzoylpyridine with *p*-(trimethylsilyl)phenyllithium gave the tertiary carbinol, m.p. 74–76°, hydrochloride, m.p. 171–173° (*211*).

J. TABLES

TABLE VII-1. Reactions of 2-Pyridyllithium with Aldehydes and Ketones



R	R′	Ref.
H	cyclohexyl	150
H	Ph[a]	150
H	*p*-tolyl	150
H	*p*-*i*-propylphenyl	150
H	*o*-chlorophenyl	150
H	*p*-chlorophenyl	150
H	3,4-dichlorophenyl	150
H	*o*-hydroxyphenyl	150
H	*p*-hydroxyphenyl	150
H	o-methoxyphenyl	150
H	*p*-methoxyphenyl	150
H	*p*-dimethylaminophenyl	150
H	2-Py	150
Me	*o*-aminophenyl	117
Me	2-amino-5-chlorophenyl	117
Et	o-aminophenyl	117
$Me_2NCH_2CH_2$	Ph	2,3,201
$Me_2NCH_2CH_2$	*p*-chlorophenyl	2,3
$Me_2NCH_2CH_2$	*p*-methoxyphenyl	2,3
$Me_2NCH_2CH_2$	2-thenyl	2,3
$Et_2NCH_2CH_2$	*p*-chlorophenyl	2,3
Pyrrolidinoethyl	*p*-chlorophenyl	2,3
Piperidinoethyl	*p*-chlorophenyl	2,3
Morpholinoethyl	*p*-bromophenyl	2,3
Ph	2-Py	174
2-Py	2-Py	174

[a] Reacted with 3-methyl-2-pyridyllithium to give 3-methyl-α-phenyl-2-pyridinemethanol.

TABLE VII-2. Miscellaneous Reactions of 2-Pyridyllithium

Reactant	Product	Ref.
CO_2	6-bromopicolinic acid[a]	73
$PhCO_2Et$	2-PyCOPh + $(2\text{-Py})_2C(OH)Ph$	174
$(PhCO)_2O$	2-PyCOPh + $(2\text{-Py})_2C(OH)Ph$	174
2-PyCO_2Et	$(2\text{-Py})_2CO$ + $(2\text{-Py})_3COH$	174
EtCN	2-PyCOEt	174
PhCN	2-PyCOPh	70,174
p-$MeOC_6H_4CN$	*p*-$MeOC_6H_4COPy\text{-}2$	70
2-PyCN	$(2\text{-Py})_2CO$	174
4-PyCN	2-PyCOPy-4	70,174
Quinoline	2-(2-pyridyl)quinoline	70
$TlCl_3$	$(2\text{-Py})_2TlCl$	1
$HgCl_2$	$(2\text{-Py})_2Hg$	70
$Me_2NCH_2CH_2Cl$	$2\text{-PyCH}[(CH_2)_2NMe_2]CH_2Ph$[b]	201
$CF_2:CFCl$	2-PyCF : CFCl	208
$CF_2:CF_2$	2-PyCF : CFPy-2	208

[a] From 6-bromo-2-pyridyllithium.

[b] From 2-PyCH(Li)CH_2Ph.

TABLE VII-3. Reactions of 3-Pyridyllithium

Reactant	Product	Ref.
CO_2	$3\text{-}PyCO_2H$	72
CO_2	5-bromonicotinic acid[a]	73
$C^{13}O_2$	$3\text{-}PyC^{13}O_2H$	14
$C^{14}O_2$	$3\text{-}PyC^{14}O_2H$	113
PhCHO	3-PyCH(OH)Ph	73
Et_2CO	$3\text{-}PyC(OH)Et_2$	63,174
Cyclohexanone	1-(3-pyridyl)cyclohexanol	63
1-Butyl-4-piperidone	1-butyl-4-hydroxy-4-(3-pyridyl)piperidine	16
$o\text{-}NH_2C_6H_4COMe$	$o\text{-}NH_2C_6H_4C(OH)MePy\text{-}3$	117
$o\text{-}NH_2C_6H_4COEt$	$o\text{-}NH_2C_6H_4C(OH)EtPy\text{-}3$	117
$Me_2NCH_2CH_2COPh$	$Me_2NCH_2CH_2C(OH)PhPy\text{-}3$	2
Ph_2CO	$3\text{-}PyC(OH)Ph_2$	63,174
$PhCH_2CH_2COPh$	$PhCH_2CH_2C(OH)PhPy\text{-}3$	63
PhCH : CHCOPh	$3\text{-}PyCHPhCH_2COPh$	63
$PhCO_2Et$	$(3\text{-}Py)_2C(OH)Ph$	174
$3\text{-}PyCO_2Et$	$(3\text{-}Py)_2CO + (3\text{-}Py)_3COH$	174
$4\text{-}PyCO_2Et$	3-PyCOPy-4	174
PhCN	PhCOPy-3	63,174
$m\text{-}MeC_6H_4CN$	$m\text{-}MeC_6H_4COPy\text{-}3$	63
$p\text{-}MeC_6H_4CN$	$p\text{-}MeC_6H_4COPy\text{-}3$	63
$p\text{-}ClC_6H_4CN$	$p\text{-}ClC_6H_4COPy\text{-}3$	63
2-Naphthonitrile	$2\text{-}C_{10}H_7COPy\text{-}3$	63
3-PyCN	$(3\text{-}Py)_2CO$	174

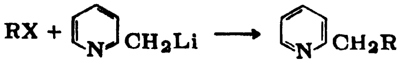
[a] From 5-bromo-3-pyridyllithium.

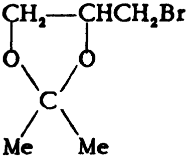
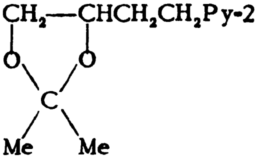
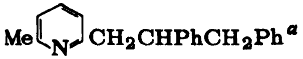
TABLE VII-4. Reactions of 4-Pyridyllithium

Reactant	Product	Ref.
$PhCO_2Et$	4-PyCOPh	193
PhCN	4-PyCOPh	193
$1\text{-}C_{10}H_7CN$	$4\text{-}PyCOC_{10}H_7\text{-}1$	193
PhCOPh	$4\text{-}PyC(OH)Ph_2$	193
$4\text{-}PyCO_2Et$	$(4\text{-}Py)_2CO$	193
2-PyCN	4-PyCOPy-2	193
3-PyCN	4-PyCOPy-3	193
4-PyCN	$(4\text{-}Py)_2CO$	193
$2\text{-}PyCO_2Et$	4-PyCOPy-2	193
$3\text{-}PyCO_2Et$	4-PyCOPy-3	193

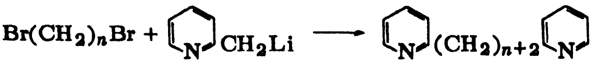
TABLE VII-5. Reactions of 2-Picolyllithium with Halides

A. Monohalides.



RX	Product	Ref.
PrBr	PrCH$_2$Py-2	54,205
i-PrBr	*i*-PrCH$_2$Py-2	53,205
MeI	2-PyEt *or* 2-Py-*i*-Pr	205
EtI	2-PyPr	205
CH$_2$: CHCH$_2$Br	2-Py(CH$_2$)$_2$CH : CH$_2$	198
CH : CCH$_2$Br	2-Py(CH$_2$)$_2$C ⋮ CH *and/or* 2-PyCH$_2$CH : C : CH$_2$	198
BuBr	2-PyC$_5$H$_{11}$	205
i-BuBr	2-Py-*i*-C$_5$H$_{11}$	205
PhCH$_2$Cl	2-Py(CH$_2$)$_2$Ph + 2-PyCH(CH$_2$Ph)$_2$	205
2-PyBr	2-PyCH$_2$Py-2	205
PyH	2-PyCH$_2$Py-2	205
(EtO)$_2$CHCH$_2$Br	(EtO)$_2$CHCH$_2$Py-2	11,166
		85
Cyclopentyl bromide	2-(cyclopentylmethyl)pyridine	127
Cyclohexyl bromide	2-(cyclohexylmethyl)pyridine	127
Cycloheptyl bromide	2-(cycloheptylmethyl)pyridine	127
Tetraacetyl-α-D-glucosyl bromide	2-PyCH$_2$COMe + (2-PyCH$_2$)$_2$C(OH)Me(?)	88
PhCHClCH$_2$Ph		92
Ph(CH$_2$)$_3$Br	Ph(CH$_2$)$_4$Py-2	160
Ph(CH$_2$)$_4$Br	Ph(CH$_2$)$_5$Py-2	160

B. Dihalides.



n	Ref.
3	90
4	90
5	90
6	90

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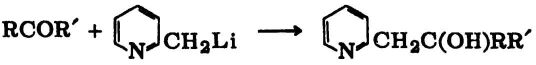
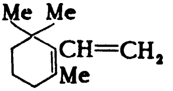
[a] From 6-methyl-2-picolyllithium.

TABLE VII-6. Reactions of 2-Picolyllithium with Aldehydes and Ketones



R	R′	Ref.
H	H	61,116
H	Me	116,158,159
H	MeCH : CH	4,57
H	MeCH : CHCH : CH	4,57
H	$EtOCH_2CH_2$	27
H	3-cyclohexenyl	138
H	Ph	17
Me		4,57
Me	*o*-aminophenyl	117
Me	2-Py	74
Et	C_8H_{37}	138
i-Pr	Ph	138
i-Bu	*i*-Bu	138
t-Bu	*t*-Bu	138
C_5H_{11}	Ph	138
Cyclopentyl	Ph	138
C_6H_{13}	C_6H_{13}	138
C_6H_{13}	cyclohexyl	138
C_6H_{13}	Ph	138
Cyclohexyl	cyclohexyl	138
Cyclohexyl	Ph	138
C_7H_{15}	C_7H_{15}	138
1-Methyl-3-*i*-propylcyclopentyl	Ph	138
Ph	4-methylcyclohexyl	138
Ph	cycloheptyl	138
Ph	bicyclo[2,2,1]-5-hepten-2-yl	138
Ph	C_8H_{17}	138
Ph	$C_{11}H_{23}$	138
Ph	Ph	42
Ph	*o*-aminophenyl	42
Ph	2-chloro-5-aminophenyl	117
p-Tolyl	*p*-aminophenyl	117

(*continued*)

TABLE VII-6. Reactions of 2-Picolyllithium with Aldehydes and Ketones (*continued*)

B. Reaction with Cyclic Ketones

Cyclic ketone	Ref.
Cyclopentanone	127
Cyclohexanone	127
Cycloheptanone	127
1-Butyl-4-piperidone	16
2-Cyclohexylcyclohexanone	138
2-(*p*-Anisyl)cyclohexanone	138
1-Indanone	138
1-Acenaphthenone	138
9-Xanthone	138
Fluorenone	138
d-Bornylone	138
d,l-Fenchilone	138

TABLE VII-7. Reactions of 2-Picolyllithium with Esters

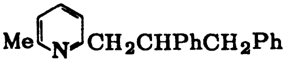
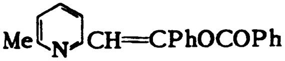
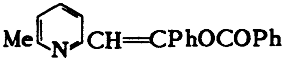
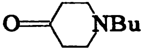
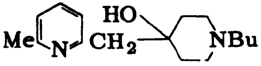
$RCO_2Me + 2\text{-}PyCH_2Li \longrightarrow 2\text{-}PyCH_2COR\ [+(2\text{-}PyCH_2)_2C(OH)R]$
(or RCO_2Et)

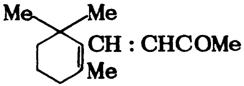
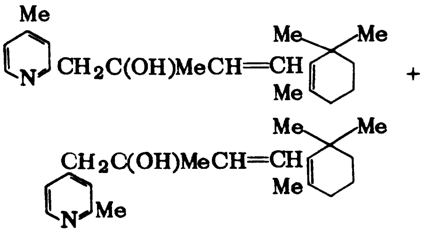
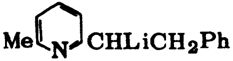
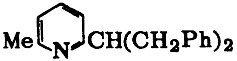
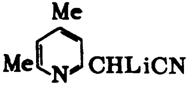
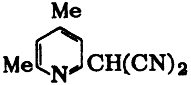
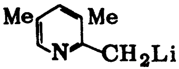
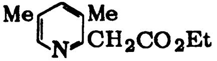
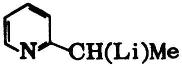
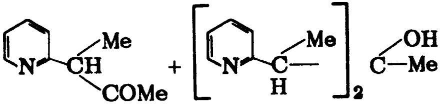
R	Product	Ref.
EtO	$2\text{-}PyCH_2COOEt$	78
Me	ketone and carbinol	12,13,76,200,203
Et	ketone and carbinol	76,200
Me_2CH	ketone and carbinol	76
Me_2CHCH_2	ketone and carbinol	76
$EtOCH_2$	ketone	180
Ph	ketone	76,203
$4\text{-}H_2NC_6H_4$	ketone	200
$4\text{-}HOC_6H_4$	ketone	200
$4\text{-}MeOC_6H_4$	ketone	200
$4\text{-}MeC_6H_4$	ketone	200
$4\text{-}FC_6H_4$	ketone	200
$2\text{-}ClC_6H_4$	ketone	200
$4\text{-}ClC_6H_4$	ketone	200
$4\text{-}BrC_6H_4$	ketone	200
$3\text{-}ClC_6H_4$	ketone	200
1-Naphthyl	ketone	200
2-Furyl	ketone	76,200
2-Thenyl	ketone	76
2-Py	ketone	77
3-Py	ketone	77
4-Py	ketone	77

TABLE VII-8. Miscellaneous Reactions of 2-Picolyllithium

Reactant	Product	Ref.
O_2	2-PyCH$_2$OH	59
Br_2	2-PyCH$_2$CH$_2$ Py-2	37
CO_2	2-PyCH$_2$COOH	25,56,79,185
Ethylene oxide	2-Py(CH$_2$)$_3$OH	74,116
Cyclohexene oxide	2-(2-picolyl)cyclohexanol	127
PhNMeCN	2-PyCH$_2$CN	105
CH$_3$COCl	2-PyCH$_2$COMe + (2-PyCH$_2$)$_2$C(OH)Me	74,97
EtOCH$_2$COCl	2-PyCH$_2$COCH$_2$OEt	180
PhCOCl	2-PyCH$_2$COPh	17
(CH$_3$CO)$_2$O	2-PyCH$_2$COMe	151,166,175
(PhCO)$_2$O	2-PyCH$_2$COPh + 2-PyCH : CPhOCOPh	92,97,154
CH$_3$CN	2-PyCH$_2$COMe	173
PhCN	2-PyCH$_2$COPh	173
2-PyCN	2-PyCH$_2$COPy-2	173
3-PyCN	2-PyCH$_2$COPy-3	33

TABLE VII-9. Reactions of Substitution Products of 2-Picolyllithium

Lithium compound	Reactant	Product	Ref.
6-Methyl-2-picolyllithium	$PhCH_2Cl$	6-methyl-2-phenethylpyridine	17,92
6-Methyl-2-picolyllithium	$PhCHClCH_2Ph$		92
6-Methyl-2-picolyllithium	CH_3CO_2Me	6-methyl-2-acetonylpyridine	77
6-Methyl-2-picolyllithium	$EtCO_2Me$	6-methyl-2-(propionylmethyl)pyridine	77
6-Methyl-2-picolyllithium	$PrCO_2Me$	6-methyl-2-(butyrylmethyl)pyridine	77
6-Methyl-2-picolyllithium	Me_2CHCO_2Me	6-methyl-2-(*i*-butyrylmethyl)pyridine	77
6-Methyl-2-picolyllithium	$PhCO_2Me$	6-methyl-2-(benzoylmethyl)pyridine	77,200
6-Methyl-2-picolyllithium	*m*-$ClC_6H_4CO_2Me$	6-methyl-2-(3-chlorobenzoylmethyl)pyridine	200
6-Methyl-2-picolyllithium	2-$C_4H_3OCO_2Me$	6-methyl-2-(2-furoylmethyl)pyridine	77
6-Methyl-2-picolyllithium	2-$C_4H_3SCO_2Me$	6-methyl-2-(2-thenoylmethyl)pyridine	77
6-Methyl-2-picolyllithium	2-$PyCO_2Me$	6-methyl-2-(picolinoylmethyl)pyridine	77
6-Methyl-2-picolyllithium	3-$PyCO_2Me$	6-methyl-2-(nicotinoylmethyl)pyridine	77
6-Methyl-2-picolyllithium	4-$PyCO_2Me$	6-methyl-2-(isonicotinoylmethyl)pyridine	77
6-Methyl-2-picolyllithium	$(PhCO)_2O$		92,97
6-Methyl-2-picolyllithium	$PhCO_2Me + PhCOCl$		194
6-Methyl-2-picolyllithium	MeCN	6-methyl-2-acetonylpyridine	32
6-Methyl-2-picolyllithium	PhCN	6-methyl-2-(benzoylmethyl)pyridine	92
6-Methyl-2-picolyllithium			16
Dilithio-2,6-lutidine	EtBr	2,6-dipropylpyridine	18
3-Methyl-2-picolyllithium	HCHO	3-methyl-2-pyridineëthanol	61
4-Methyl-2-picolyllithium	methyl benzoate	4-methyl-2-(benzoylmethyl)pyridine	200
4-Methyl-2-picolyllithium	methyl 3-chlorobenzoate	4-methyl-2-(3-chlorobenzoylmethyl)pyridine	200

5-Ethyl-2-picolyllithium	MeCN	5-ethyl-2-acetonylpyridine	32
5-Ethyl-2-picolyllithium	ethylene oxide	5-ethyl-2-pyridinepropanol	128
4,6-Dimethyl-2-picolyllithium	PhNMeCN	4,6-dimethyl-2-pyridineacetonitrile	105
Mixture of 4-methyl-2-picolyllithium and 2-methyl-4-picolyllithium			4,57
2-PyCHLi(CH$_2$)$_3$Me	MeCN	2-PyCH(COMe$_3$)(CH$_2$)$_3$Me	32
	PhCH$_2$Cl		92
5-Nitro-2-picolyllithium	EtBr	5-nitro-2-propylpyridine	79
5-Ethoxy-2-picolyllithium	EtBr	5-ethoxy-2-propylpyridine	79
2-PyCHLiCN	PhNMeCN	2-PyCH(CN)$_2$	105
	PhNMeCN		105
	(EtO)$_2$CO		199
	CH$_3$CO$_2$Me		203

(continued)

TABLE VII-9. Reactions of Substitution Products of 2-Picolyllithium (*continued*)

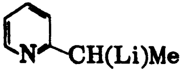
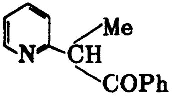
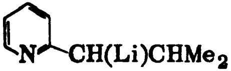
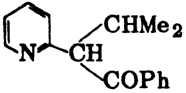
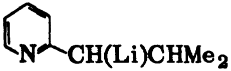
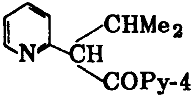
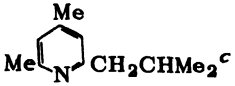
Lithium compound	Reactant	Product	Ref.
	$PhCO_2Me$		203
	$PhCO_2Me$		203
	4-$PyCO_2Me$		203

TABLE VII-10. Reactions of 4-Picolyllithium

Reactant	Product	Ref.
CO$_2$	4-PyCH$_2$COOH	84,169
CO$_2$	2-Phenyl-4-pyridineacetic acid	129
EtBr	4-PyPr (+4-methyl-2-phenylpyridine and 4-propyl-2-phenylpyridine)	171,205
PrBr	4-PyBu	171,205
i-PrBr	4-PyBu-*i*	205
BuBr	4-PyC$_5$H$_{11}$	171,205
BuBr	4-PyCHBuMe[a]	171
C$_5$H$_{11}$Br	4-PyC$_6$H$_{13}$	171
C$_6$H$_{13}$Br	4-PyC$_7$H$_{15}$	171
C$_7$H$_{15}$Br	4-PyC$_8$H$_{17}$	171
C$_8$H$_{17}$Br	4-PyC$_9$H$_{19}$	171
C$_9$H$_{19}$Br	4-PyC$_{10}$H$_{21}$	171
PhCH$_2$Cl	4-Py(CH$_2$)$_2$PhMe	205
CH$_3$COBr	4-PyCH$_2$COMe	84,169
CH$_3$CO$_2$Et	4-PyCH$_2$COMe	169,206
BrCH$_2$CH(OEt)$_2$	4-PyCH$_2$CH$_2$CH(OEt)$_2$	84,169
PhCO$_2$Me	4-PyCH$_2$COPh	206
4-PyCO$_2$Me	4-PyCH$_2$COPy-4	206
C$_2$H$_5$CO$_2$Me	4-PyCH$_2$COEt	206
i-C$_3$H$_7$CO$_2$Me	4-PyCH$_2$CO-*i*-C$_3$H$_7$	206
Me$_3$CCO$_2$Me	4-PyCH$_2$COCMe$_3$	206
PhCO$_2$Me	4-PyCHMeCOPh[a]	206

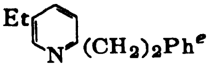
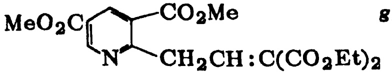
[a] From 4-PyCHLiMe.

TABLE VII-11. Reactions of 2-Picolylsodium

Reactant	Product	Ref.
MeCl	2-PyEt + 2-PyCHMe$_2$	30,39
MeCl	2-PyCHMe$_2$[a]	30
MeCl	2-PyCMe$_3$[b]	30
MeI	2-PyEt + 2-PyCHMe$_2$	30
EtBr	2-PyPr	30
PrCl	2-PyBu	39,43
i-PrCl		43
i-BuCl	2-PyCH$_2$CH$_2$CHMe$_2$	39
Cyclopentyl chloride	2-(cyclopentylmethyl)pyridine	40,43
Cyclohexyl chloride	2-(cyclohexylmethyl)pyridine	40,43
Cyclohexyl bromide	2-(cyclohexylmethyl)pyridine	39

(*continued*)

TABLE VII-11. Reactions of 2-Picolylsodium (*continued*)

Reactant	Product	Ref.
2-Methylcyclohexyl chloride	2-(2-methylcyclohexylmethyl)pyridine	49
4-Ethylcyclohexyl chloride	2-(4-ethylcyclohexylmethyl)pyridine	49
$C_{12}H_{25}Cl$	2-$PyC_{13}H_{27}$	98
$C_{14}H_{29}Cl$	2-$PyC_{15}H_{31}$	98
$C_{16}H_{33}Cl$	2-$PyC_{17}H_{35}$	40,98
$C_{18}H_{37}Cl$	2-$PyC_{19}H_{39}$	98
$CHCl:CCl_2$	2-$PyCH_2CH:CCl_2$[d]	41,43
$CH_2ClCH:CH_2$	2-$PyCH_2CH_2CH:CH_2$	39
$Cl(CH_2)_9CH:CH_2$	2-$Py(CH_2)_{10}CH:CH_2$	31
$PhCH_2Cl$	2-$Py(CH_2)_2Ph$ + 2-$PyCH(CH_2Ph)_2$	39
$PhCH_2Cl$		39,43
$Ph(CH_2)_2Cl$	2-$Py(CH_2)_3Ph$ + 2-$PyCH(CH_2CH_2Ph)_2$	40,43
$EtOCH_2CH_2Cl$	2-$Py(CH_2)_3OEt$	41
$(EtO)_2CHCH_2Cl$	2-$Py(CH_2)_2CH(OEt)_2$	41
$Me_2NCH_2CH_2Cl$	2-$Py(CH_2)_3NMe_2$	201
$Et_2NCH_2CH_2Cl$	2-$Py(CH_2)_3NEt_2$	41,43
$Me_2NCH_2CH_2Cl$	2-$PyCHPh(CH_2)_2NMe_2$[f]	201
p-$NH_2C_6H_4COC_6H_4OMe$-*p*	2-$PyCH_2C(OH)$(*p*-$NH_2C_6H_4)C_6H_4OMe$-*o*	118
$(CH_3CO)_2O$	2-$PyCH_2COMe$	134
$(EtCO)_2O$	2-$PyCH_2COEt$	134
MeCN	2-$PyCH_2COMe$	134
$EtOCH:C(CO_2Et)_2$	2-$PyCH_2CH:C(CO_2Et)_2$[g]	199
$EtOCH:C(CO_2Et)_2$	 [g,h]	199
$PhCO_2Me$	2-$PyCH_2COPh$	203
$PhCO_2Me$	2-$PyCH(Me)COPh$[i]	203

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[a] From 2-PyCHNaMe.

[b] From 2-$PyCNaMe_2$.

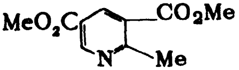
[c] From 4,6-dimethyl-2-picolylsodium.

[d] Structure not established; product polymerizes readily.

[e] From 5-ethyl-2-picolylsodium.

[f] From 2-$PyCH_2Ph$.

[g] This intermediate not isolated.

[h] From 

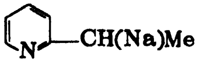
[i] From 

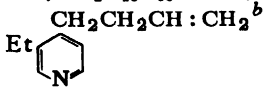
TABLE VII-12. Reactions of 3-Picolylsodium

Reactant	Product	Ref.
MeCl	3 -$PyCH_2Me$ + 3-$PyCHMe_2$ + 3-$PyCMe_3$	30
MeCl	3-$PyCHMe_2$[a]	30
MeCl	3-$PyCMe_3$[b]	30
EtBr	3-PyPr	209
PrBr	3-PyBu	209
BuBr	3-PyC_5H_{11}	209
n-$C_5H_{11}Br$	3-PyC_6H_{13}	209
o-$NH_2C_6H_4COC_6H_4OMe$-*p*	3-$PyCH_2C(OH)$(*o*-$NH_2C_6H_4$)C_6H_4OMe-*p*	118

[a] From 3-PyCHNaMe.

[b] From 3-$PyCNaMe_2$.

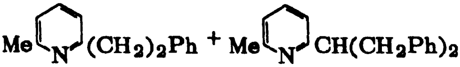
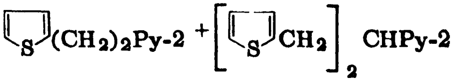
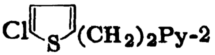
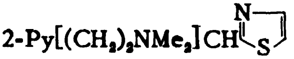
TABLE VII-13. Reactions of 4-Picolylsodium

Reactant	Product	Ref.
MeCl	4-PyEt + 4-$PyCHMe_2$ + 4-$PyCMe_3$	30
EtCl	4-PyPr	39,126
EtBr	4-PyPr + 4-$PyCHEt_2$	40,43
EtBr	4-PyCHMeEt[a]	39,43
Et_2SO_4	4-PyPr	43
i-PrCl	4-$PyCH_2$(*i*-Pr)	43
BuCl	4-$PyCH_2Bu$ + 4-$PyCHBu_2$	39
i-BuCl	4-$PyCH_2Bu$-*i* + 4-PyCH(Bu-*i*)$_2$	39,43
p-$MeC_6H_4SO_3$(*i*-Bu)	4-$PyCH_2Bu$-*i*	43
Cyclohexyl chloride	4-(cyclohexylmethyl)pyridine	40,43
2-Methylcyclohexyl bromide	4-(2-methylcyclohexylmethyl)pyridine	49
4-Ethylcyclohexyl bromide	4-(4-ethylcyclohexylmethyl)pyridine	49
Hexadecyl chloride	4-$PyCH_2C_{16}H_{33}$ + 4-$PyCH(C_{16}H_{33})_2$	40
$CH_2:CHCH_2Br$	[b]	39,43
$PhCH_2Cl$	4-$PyCH_2CH_2Ph$ + 4-$PyCH(CH_2Ph)_2$	39,43
$EtO(CH_2)_2Cl$	4-$Py(CH_2)_3OEt$	41
$(EtO)_2CHCH_2Cl$	4-$Py(CH_2)_2CH(OEt)_2$	41,43
$Et_2N(CH_2)_2Cl$	4-$Py(CH_2)_3NEt_2$	41

[a] From 4-PyCHNaMe.

[b] From 3-ethyl-4-picolylsodium.

TABLE VII-14. Reactions of 2-Picolylpotassium

Reactant	Product	Ref.
Cyclohexyl bromide	2-(cyclohexylmethyl)pyridine	150
$MeO(CH_2)_2Cl$	$2\text{-}Py(CH_2)_3OMe$	116
$MeO(CH_2)_3Cl$	$2\text{-}Py(CH_2)_4OMe$	116
$MeO(CH_2)_5Br$	$2\text{-}Py(CH_2)_6OMe$	116
$MeO(CH_2)_6Br$	$2\text{-}Py(CH_2)_7OMe$	116
$Me_2N(CH_2)_2Cl$	$2\text{-}Py(CH_2)_3NMe_2$	201
$Me_2N(CH_2)_2Cl$	$2\text{-}PyCH[(CH_2)_2NMe_2]C_6H_4Me\text{-}p^c$	201
PhCl	$2\text{-}PyCH_2Ph + 2\text{-}PyCPh_3$	55
$PhCH_2Cl$	$2\text{-}Py(CH_2)_2Ph + 2\text{-}PyCH(CH_2Ph)_2$	22
$PhCH_2Cl$	2-phenethyl-5-ethylpyridine[a]	43
$PhCH_2Cl$	 [b]	39,43
$p\text{-}MeOC_6H_4CH_2Cl$	$p\text{-}MeOC_6H_4(CH_2)_2Py\text{-}2$	22
$Ph(CH_2)_3Cl$	$2\text{-}Py(CH_2)_4Ph$	22
1-Naphthylmethyl chloride	$1\text{-}C_{10}H_7(CH_2)_2Py\text{-}2$	22
2-Thenyl chloride		150
5-Chloro-2-thenyl chloride		150
2-Chlorothiazole	 [d]	201
$(EtO)_2CO$	$2\text{-}PyCH_2CO_2Et$	163
$EtOCH_2CO_2Et$	$2\text{-}PyCH_2COCH_2OEt$	180
EtBr	$2\text{-}PyC(Et)[(CH_2)_2NMe_2](CH_2)_2Ph^e$	201

[a] From 5-ethyl-2-picolylpotassium.
[b] From 6-methyl-2-picolylpotassium.
[c] From $2\text{-}PyCH_2C_6H_4Me\text{-}p$.
[d] From $2\text{-}Py(CH_2)_3NMe_2$.
[e] From $2\text{-}PyCH[(CH_2)_2NMe_2]_2\ (CH_2)_2Ph$.

TABLE VII-15. Reactions of 3-Picolylpotassium

Reactant	Product	Ref.
$PhCO_2Me$	3-$PyCH_2COPh$	204
$PhCH_2Cl$	3-$Py(CH_2)_2Ph$ + 3-$PyCH(CH_2Ph)_2$	204
p-$MeOC_6H_4CO_2Me$	3-$PyCH_2COC_6H_4OMe$-*p*	204
3-$PyCO_2Me$	3-$PyCH_2COPy$-3	204
4-$PyCO_2Me$	3-$PyCH_2COPy$-4	204
Methyl 2-furoate	3-$PyCH_2COC_4H_3O$-2	204
Methyl 2-thiophenecarboxylate	3-$PyCH_2COC_4H_3S$-2	204
EtBr	3-PyPr	207
$CH_2:CHCH_2Cl$	3-$Py(CH_2)_2CH:CH_2$	207
i-PrBr	3-$PyCH_2CHMe_2$	207
PrBr	3-PyBu	207
BuBr	3-$Py(CH_2)_4Me$	207
$Me(CH_2)_4Br$	3-$Py(CH_2)_5Me$	207
Me_2CHCH_2Br	3-$Py(CH_2)_2CHMe_2$	207
Cyclopentyl bromide	3-$PyCH_2CH(CH_2)_4$	207
$Me_2N(CH_2)_2Cl \cdot HCl$	3-$Py(CH_2)_3NMe_2$	207
$Et_2N(CH_2)_2Cl \cdot HCl$	3-$Py(CH_2)_3NEt_2$	207

TABLE VII-16. Reactions of 4-Picolylpotassium

Reactant	Product	Ref.
$MeO(CH_2)_2Cl$	4-$Py(CH_2)_3OCH_3$	116
$Br(CH_2)_3Br$	4-$Py(CH_2)_5$ Py-4	90
$Br(CH_2)_4Br$	4-$Py(CH_2)_6Py$-4	90
$Br(CH_2)_5$ Br	4-$Py(CH_2)_7Py$-4	90
$Br(CH_2)_6Br$	4-$Py(CH_2)_8Py$-4	90
$PhCH_2Cl$	4-$Py(CH_2)_2Ph$	22
$Ph(CH_2)_2Cl$	4-$Py(CH_2)_3Ph$	22
$Ph(CH_2)_3Cl$	4-$Py(CH_2)_4Ph$	22
o-$ClC_6H_4CH_2Cl$	*o*-$ClC_6H_4(CH_2)_2Py$-4	22
p-$MeOC_6H_4CH_2Cl$	*p*-$MeOC_6H_4(CH_2)_2Py$-4	22
1-Chloromethylnaphthalene	1-$C_{10}H_7(CH_2)_2Py$-4	22
4-PyCl	$(4\text{-}Py)_2CH_2$	90
4-$Py(CH_2)_2Br$	4-$Py(CH_2)_4Py$-4	90

TABLE VII-17. Reactions of Pyridylmagnesium and Picolylmagnesium Halides with Aldehydes and Ketones

$$\text{PyMgX} + \text{RCOR}' \longrightarrow \text{PyC(OH)RR}'$$

PyMgX	R	R′	Ref.
2-PyMgBr	H	Et	149
3-PyMgBr	H	C_6H_{13}	176
2-PyMgBr	H	Ph	120,131,149
3-Methyl-2-pyridylmagnesium bromide	H	Ph	99
4-Methyl-2-pyridylmagnesium bromide	H	Ph	99
6-Methyl-2-pyridylmagnesium bromide	H	Ph	99
3-PyMgBr	H	Ph	120,149
2,6-Pyridyldimagnesium dibromide	H	Ph	131
2-PyMgBr	H	*m*-MeC_6H_4	149
2-PyMgBr	H	*p*-MeC_6H_4	149
2-PyMgBr	H	*p*-(*i*-Pr)C_6H_4)	149
2-PyMgBr	H	*p*-MeOC_6H_4	149
2-PyMgBr	H	3,4-methylenedioxyphenyl	149
2-PyMgBr	H	*p*-$Me_2NC_6H_4$	149
2-PyMgBr	H	2-thenyl	149
2-PyMgBr	H	$PhCH_2$	149
2-PyMgBr	H	$Ph(CH_2)_2$	149
2-PyMgBr	Me	Ph	131
3-PyMgBr	Me	Ph	177
2-PyMgBr	Ph	Ph	7,131,155
3-PyMgBr	Ph	Ph	63,177
4-PyMgCl	H	H	193
4-PyMgCl	Me	Me	193
4-PyMgCl	H	Ph	193
4-PyMgCl	Me	Ph	193
4-PyMgCl	Ph	Ph	193
2-$PyCH_2MgBr$	Me	Me	196
2-$PyCH_2MgBr$	Me	Et	196
2-$PyCH_2MgBr$	Me	Ph	196
2-$PyCH_2MgBr$	H	Me	196
2-$PyCH_2MgBr$	H	Ph	196
2-$PyCH_2MgBr$	H	2-Py	196

TABLE VII-18. Miscellaneous Reactions of Pyridylmagnesium and Picolylmagnesium Halides

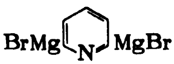
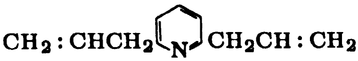
PyMgX	Reactant	Product	Ref.
3-PyMgBr	$CH_2:CHCH_2Br$	3-Py$CH_2CH:CH_2$	160,176
3-PyMgBr	$CH_2:CMeCH_2Cl$	3-Py$CH_2CMe:CH_2$	177
2-PyMgBr	$HC(OEt)_3$	2-Py$CH(OEt)_2$	172
3-PyMgBr	$HC(OEt)_3$	3-Py$CH(OEt)_2$	172,176
4-PyMgCl	$HC(OEt)_3$	4-Py$CH(OEt)_2$	82
2-PyMgBr	MeCOCl	2-PyCOMe + $(2\text{-}Py)_2C(OH)$-Me	74
2-PyMgI	MeCOCl	2-PyCOMe + $(2\text{-}Py)_2C(OH)$-Me	74
3-PyMgBr	$(MeCO)_2O$	3-PyCOMe	176
3-PyMgBr	$PhCO_2Et$	$(3\text{-}Py)_2C(OH)Ph$	174
2-PyMgBr	2-PyCO_2Et	$(2\text{-}Py)_2CO$ + $(2\text{-}Py)_3COH$	94
2-PyMgBr	PhCN	2-PyCOPh	94
2-PyMgBr	Ph_2PbI_2	2-Py$Pb(Ph)_2I$	70
2-PyMgBr	Ph_3PbI	No reaction	70
2-PyMgBr	$CH_2:CHCH_2Br$	2-Py$CH(CH:CH_2)CH_2CH:CH_2$	198
2-PyMgBr	$CH_2:CHCH_2Br$	2-Py$CH_2CH:CH_2$	210
	$CH_2:CHCH_2Br$		210
2-PyMgBr	$HC\vdots CCH_2Br$	2-Py$CH(COMe)CH_2C\vdots CH$	198
2-PyCH_2MgBr	$MeCO_2Et$	2-PyCH_2COMe + $(2\text{-}PyCH_2)_2$-C(OH)Me	196
2-PyCH_2MgBr	2-PyCO_2Et	2-PyCH_2COPy-2 + $(2\text{-}PyCH_2)_2C(OH)$Py-2	196
2-PyCH_2MgBr	$PhCO_2Et$	$(2\text{-}PyCH_2)_2C(OH)Ph$ + 2-PyCH_2COPh	196
4-PyMgCl	$HC(OEt)_3$	4-Py$CH(OEt)_2$	193
4-PyMgCl	$PhCONH_2$	4-PyCOPh	193

TABLE VII-19. Mercury Derivatives of Pyridine

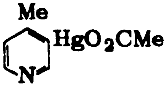
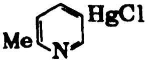
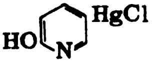
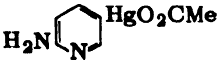
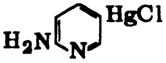
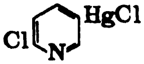
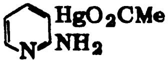
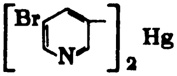
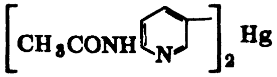
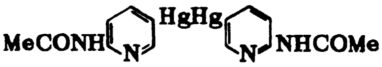
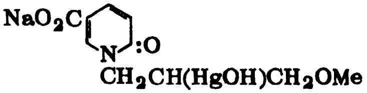
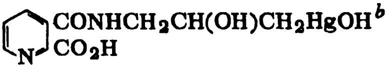
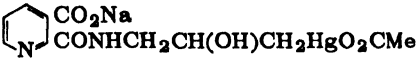
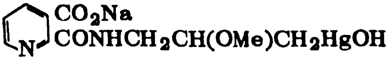
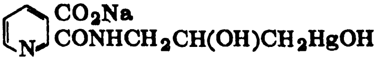
Compound	Melting point, °C.	Ref.
3-PyHgO_2CMe	177–78	89,121,122, 135,140–142
3-PyHg$O_2CC_{17}H_{35}$		152
3-PyHgCl	279.5–80.0	89,96,109, 115,135, 153,195
3-PyHgBr	271–72	96,115
3-PyHgI	270 (dec.)	115
3-PyHgNO_3	> 360	140,141,153
	148–50	50
		153
	236	6,26
	160–62	114,162
	197.5	153
	263	195
	206–9	162
(2-Py)$_2$Hg	198–200	70
(3-Py)$_2$Hg	239	195
	225–27 (dec.)	15
	230	162
3-PyHgPh	174–75	115
		123

TABLE VII-19. (*Continued*)

Compound	Melting point, °C.	Ref.
 NaO_2C, :O, $\text{CH}_2\text{CH(HgOH)CH}_2\text{OMe}$		36,87
$3\text{-PyCONHCH}_2\text{CH(OH)CH}_2\text{HgO}_2\text{CMe}$	160–70 (dec.)	144,145,163
$3\text{-PyCONHCH}_2\text{CH(OH)CH}_2\text{HgOH}$[a]	115–20 (dec.)	144,145
 $\text{CONHCH}_2\text{CH(OH)CH}_2\text{HgOH}$[b] CO_2H	205 (dec.)	144,145
 CO_2Na $\text{CONHCH}_2\text{CH(OH)CH}_2\text{HgO}_2\text{CMe}$	163	164
 CO_2Na $\text{CONHCH}_2\text{CH(OMe)CH}_2\text{HgOH}$		164
 CO_2Na $\text{CONHCH}_2\text{CH(OH)CH}_2\text{HgOH}$		164
$3\text{-PyCONHCONHCH}_2\text{CH(OH)CH}_2\text{HgO}_2\text{CMe}$	145–55	164

[a] Tartrate, m.p. 140° (dec.); benzoate, m.p. 55–60°; theophylline salt, m.p. 120° (dec.).

[b] Theophylline salt, m.p. 215° (dec.).

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CHAPTER VIII

Nitropyridines and Their Reduction Products (except Amines)

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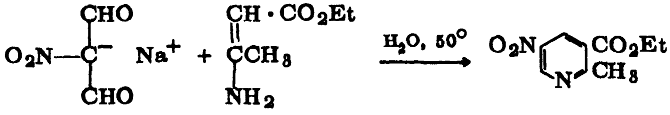
A. NITROPYRIDINES

1. Preparation

a. Synthesis from Aliphatic Intermediates

The preparation of a nitropyridine from aliphatic intermediates was first reported only recently (*55*). Sodium nitromalonaldehyde condenses with ethyl β-aminocrotonate under moderate conditions to form ethyl 2-methyl-5-nitronicotinate. Catalytic reduction of the condensation product leads to amino and hydroxylamino derivatives (VIII-1). Cyanoacetamide also reacts with this nitroaldehyde (*55a*).



(VIII-1)

b. Nitration of Pyridine and Its Homologs

The unsubstituted pyridine nucleus is resistant to nitration, which can be effected only under drastic conditions. This is explained by the formation of the positive pyridinium ion in acid nitrating media, which exerts a powerful deactivating effect by reducing the electron density throughout the ring; this effect is especially pronounced at the 2 and 4 positions (*cf.* Chapter I, p. 22).

Friedl (*57,58*) first reported the direct nitration of pyridine in 1912. He obtained a 15% yield of 3-nitropyridine with potassium nitrate and fuming sulfuric acid at 330°. Kirpal and Reiter (*104*), however, could not obtain yields greater than 1% by this procedure, but noted the beneficial effect of iron on the process. Den Hertog and Overhoff (*83*), on the other hand, could not duplicate these latter results; under similar forcing conditions, however, they obtained 2-nitropyridine along with the 3-isomer, with the proportion of 2-isomer increasing at higher temperatures.

The use of nitrogen dioxide and aluminum chloride in the nitration process leads to the known addition compound of nitrogen dioxide and pyridine (*171*). 3-Nitropyridine is formed, however, by treatment of pyridine with nitrogen dioxide and carbon dioxide at 115–120° (*172*). This reaction proceeds at 15–20° and seems to indicate a more active process than those reported previously. Explosive conditions result at elevated temperatures (300–330°), or with liquid nitrogen dioxide at room temperature.

Little work has been reported on alkylpyridines; nitration, however, seems to be facilitated by the presence of alkyl groups. Thus, 2-picoline is nitrated with difficulty and in poor yield, while 2,6-lutidine reacts below 100°, and 2,4,6-collidine even more readily (*157,167*).

The nitration of 2- and 4-phenylpyridines occurs exclusively in the benzenoid moiety (*69a*).

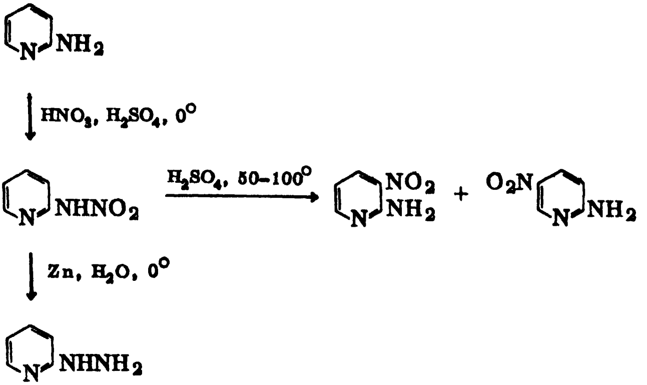
The nitration reactions of pyridine and its homologs are summarized in Table VIII-1 (p. 496). *Cf.* Chapter V, p. 190.

c. Nitration of Substituted Pyridines

(a) Aminopyridines. Aminopyridines react very readily with nitrating agents. The products derived from this process have proved to be most valuable intermediates and lead to a large variety of derivatives (*cf.* Chapter IX, Tables IX-40, IX-41, and IX-42).

The nitration of 2-aminopyridine at low temperatures leads to 2-nitraminopyridine, which is isolated with ease. This substance rearranges by treatment with concentrated sulfuric acid at 50–100°;

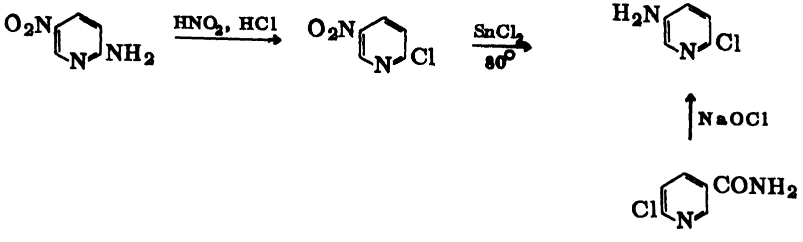
two isomeric aminonitropyridines result: 2-amino-3-nitro- and 2-amino-5-nitropyridine, the latter predominating (VIII-2) (*26,30,41, 156,162*). Phosphoric acid does not effect this transformation (*117*). Nitration at higher temperatures yields the isomeric aminonitropyridines directly.



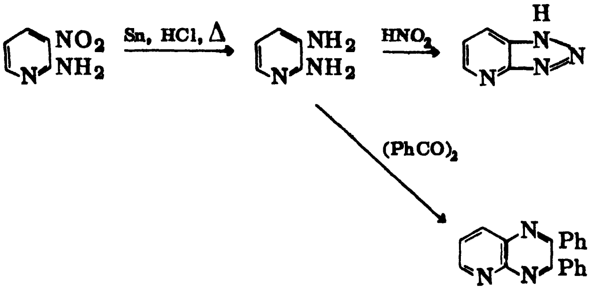
(VIII-2)

(VIII-3)

Chichibabin and Rasorenow (*41*) proved the nitramine structure by reduction to 2-hydrazinopyridine (VIII-3) and established the orientation of the isomeric nitro-2-aminopyridines as follows: 2-Amino-5-nitropyridine was converted to 5-amino-2-chloropyridine, identical to that derived from the known 6-chloronicotinamide (VIII-4). The other isomer was reduced to the diamine; this substance displayed the characteristic behavior of *o*-diamines with nitrous acid, benzil, and other reagents (VIII-5) (*33*).



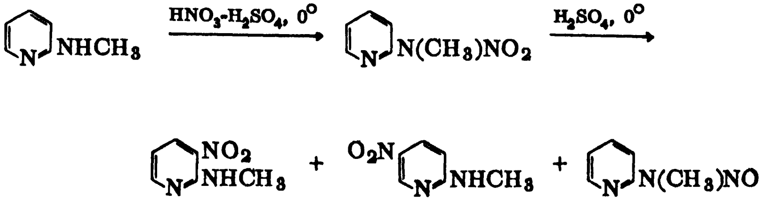
(VIII-4)



(VIII-5)

Both aminonitropyridines yield nitraminopyridines on further nitration, which undergo isomerization to 2-amino-3,5-dinitropyridine (*25,32,41*).

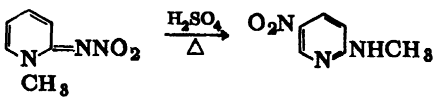
2-Methylaminopyridine undergoes a similar series of transformations, but a partial reduction to the nitrosamine seemingly occurs during the isomerization process (VIII-6). The methylaminonitro pyridines are nitrated further to nitraminonitro compounds, which undergo rearrangement to the same aminodinitropyridine (*32*).



(VIII-6)

The nitramine is not an essential intermediate in the nitration of aminopyridines. Thus, Chichibabin (*35,36*) obtained a mixture of 5- and 3-nitro-2-dimethylaminopyridines from 2-dimethylaminopyridine, where the nitramine route is clearly impossible. Further nitration of these isomers leads to the same dinitrodimethylaminopyridine.

1,2-Dihydro-2-imino-1-methylpyridine yields the nitroimine under mild nitrating conditions. The isomerization product was originally considered to be 5-nitro-1,2-dihydro-2-imino-1-methylpyridine; subsequent studies, however, have revealed a migration of the 1-methyl group to the amino substituent, yielding 2-methylamino-5-nitropyridine (VIII-7) (*32,38*).


(VIII-7)

The nitration of 6-amino-5-ethyl-2-picoline yields a mixture of the nitramine and 3-nitro compound (*44*); the nitramine, however, could not be isomerized. Similarly, 3-aminopyridine forms a nitramine which is refractory towards rearrangement; instead, hydrolysis to 3-pyridinol occurs under usual conditions (*34*).

In contrast to this behavior, the low-temperature nitration of 3-methylaminopyridine affords the nitramine, which undergoes ready conversion to 3-methylamino-2-nitropyridine (*159*).

The preparation of 4-nitraminopyridine follows conventional lines, and rearrangement to 4-amino-3-nitropyridine results on treatment with sulfuric acid. Under appropriate nitration conditions 4-nitramino-3-nitropyridine can be prepared; isomerization to 4-amino-3,5-dinitropyridine, however, requires more drastic treatment (*111,112*).

The nitration of 2,2′-dipyridylamine at 20° produces a mixture of mono- and polynitro compounds. At 0° the principal product is 5-nitro-2,2′-dipyridylamine, while at 100° good yields of 3,3′- and 5,5′-dinitro-2,2′-dipyridylamines result (*40,202*). 4,4′-Dipyridylamine nitrate undergoes conversion to 3-nitro-4,4′-dipyridylamine by treatment with sulfuric acid; nitration of the free amine with fuming nitric and sulfuric acids leads to 3,3′-dinitro-4,4′-dipyridylamine (*110*).

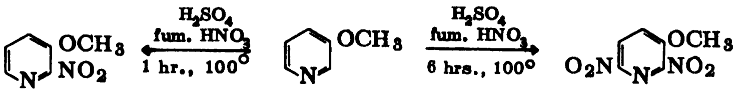
A tetranitro derivative is formed by treatment of 2,2′-diamino-5,5′-bipyridine with a cold nitrating mixture; structural determinations, however, have not been made (*93*).

(b) Pyridinols and Pyridyl Ethers. (*Cf.* Chapter XII.) The nitration of 2-pyridinol proceeds readily at moderate temperatures to a mixture of 3- and 5-nitro-2-pyridinols (*43*). Chichibabin and Schapiro obtained a substance, m.p. 286°, which was considered to be 3,5-dinitro-2-pyridinol. Subsequent work by Berrie, Newbold, and Spring (*5*) revealed this to be a mixture of 3-nitro-2-pyridinol and 3,5-dinitro-2-pyridinol (as sodium salts). The substance of m.p. 289° obtained by Takahashi and Yamamoto (*191*) is seemingly the same as that of Chichibabin and Schapiro. Further nitration of this mixture affords the dinitro compound, m.p. 175°. Plazek (*158*) obtained a dinitro-2-pyridinol, m.p. 176°, and converted it to the known 3,5-diaminopyridine by an unambiguous route to support the work of Berrie and associates.

2-Methoxypyridine has been converted to the 5-nitro compound in high yield at 100° (*227*). The isomeric 1-methyl-2(1*H*)-pyridone leads to 1-methyl-5-nitro-2(1*H*)-pyridone; thus, no migration of the methyl group occurs as with the analogous pyridonimine.

3-Pyridinol is very sensitive to nitrating acids, and at temperatures above 50° the pyridine ring undergoes cleavage. Yields of 50% of a mononitro 3-pyridinol have been obtained under controlled conditions (*211,212,222*). Plazek (*160*) has shown this product to be 2-nitro-3-pyridinol. 2-Nitro-3-pyridinol in turn gives modest yields of 2,6-dinitro-3-pyridinol with fuming nitric acid and acetic acid–acetic anhydride. 2,4,6-Trinitro-3-pyridinol occurs as a by-product in this reaction (*50a*). Weidel and Murmann (*198*) have nitrated 3-acetoxypyridine, but the nitropyridinol obtained on hydrolysis differs from that described above.

3-Alkoxypyridines are mononitrated at room temperature. Koenigs (*108*) considered the product derived from 3-ethoxypyridine to be 3-ethoxy-6-nitropyridine; den Hertog (*74*), however, has demonstrated conclusively that this substance was 3-ethoxy-2-nitropyridine. Bernstein (*4*) converted 3-methoxypyridine to 3-methoxy-2-nitropyridine, and to 3-methoxy-2,6-dinitropyridine on longer nitration. This dinitro compound, m.p. 114°, differs from that of Koenigs, m.p. 69° (VIII-8).



(VIII-8)

The nitration of 2,3′-dipyridyl ether yields exclusively the 5-nitro compounds (*203a*).

3,5-Dialkoxypyridines similarly undergo easy nitration. Thus, Koenigs (*108*) obtained 3,5-diethoxy-2,6-dinitropyridine in 60% yield. Den Hertog (*88*), however, isolated a mononitro compound under identical conditions; dinitration occurred with somewhat more drastic treatment.

The nitration of 4-pyridinol leads to 3-nitro- and 3,5-dinitro-4-pyridinols (*50,105*). Similarly, 3-nitration occurs with 2,4-pyridinediol and 2,6-pyridinediol (*60,105,114,203,218,220,235*).

Among halopyridines, only the 3-isomers undergo nitration, to yield 3-halo-5-nitropyridines (*161*).

d. From Pyridine 1-Oxides

The work of Ochiai in Japan and of den Hertog in Europe has revealed a most interesting behavior of pyridine 1-oxide in the nitration reaction (*cf.* Chapter IV, p. 122). In contrast to pyridine, the oxide undergoes easy substitution and is converted to 4-nitropyridine 1-oxide in good yield. Although substitution occurs predominantly at the 4 position, 2-nitration has been noted (*132*), with concurrent deoxygenation. The reaction proceeds readily among the homologous pyridine oxides, but no reaction occurs when the 4 position bears a methyl substituent (*90*). A 4-oxy substituent, however, leads to 3-nitro and 3,5-dinitro derivatives (*72,135*).

3,5-Diethoxypyridine 1-oxide is readily substituted under mild conditions and affords the corresponding 2-nitro compound. Under more forcing conditions the reaction product is 3,5-diethoxy-2,6-dinitropyridine. With only one alkoxy substituent, however, substitution is directed to the 4 position (*76,80*).

The removal of the oxide function is accomplished readily with such agents as phosphorus trichloride, sulfuryl chloride, thionyl chloride and acetyl chloride. Phosphorus trichloride in refluxing chloroform has been the reagent of choice and affords 4-nitropyridine in high yield. Side reactions, including the formation of 4-chloropyridine and 1-(4-pyridyl)-4(1*H*)-pyridone, have been noted with these substances (*69*).

Table VIII-2 (pp. 497 ff.) summarizes the nitration reactions of pyridine 1-oxides and the deoxygenation of the nitro derivatives.

e. From Aminopyridines

Nitropyridines have been prepared by oxidation of aminopyridines, quite often in good yields. Thus, 2-nitropyridine and homologs result from amino compounds treated with hydrogen peroxide–sulfuric acid and similar oxidants (*101,203*).

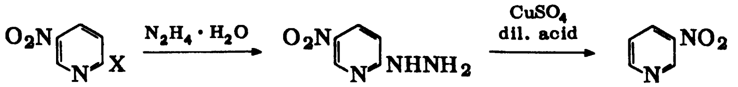
Von Schickh, Binz, and Schulz (*173*) have reported the formation of 3-nitropyridine from the amino compound; Wiley and Hartman (*203*), however, only obtained 3,3′-azoxydipyridine by this procedure. Oxidation of 3-pyridinediazonium sulfate affords the 3-nitro compound in low yield (*173*).

4-Nitropyridine results in high yield from the amino compound by oxidation (*102*), but is prepared more advantageously from the readily available 4-nitropyridine 1-oxide. 4-Aminopicolines have been oxidized to the corresponding nitropicolines with varying degrees of success (*1,18,177*).

The oxidation of aminopyridines to nitropyridines is summarized in Table VIII-3 (p. 500).

f. From Hydrazinonitropyridines

Oxidative treatment of 2-hydrazino-5-nitropyridine, readily available from the halonitropyridine, yields 3-nitropyridine (VIII-9)



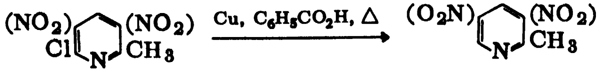
(VIII-9)

(*164,210*). Similar treatment of 2-hydrazino-3,5-dinitropyridine affords 3,5-dinitropyridine (*158*). The applications of this reaction are summarized in Table VIII-4 (p. 501).

g. From Halonitropyridines

Baumgarten, Su, and Krieger (*3*) have effected the removal of halo and hydrazino groups by various methods in preparing a number of nitropicolines.

The Smith procedure (VIII-10), which effects replacement of halogen by hydrogen via copper–benzoic acid treatment at 160–



(VIII-10)

180°, has yielded nitropyridines in yields in the range of 27–80% (*3,15*). The Blatt-Tristam method, involving treatment with sodium iodide and formic acid at 100°, has not proved fruitful. In the only successful recorded example, 6-chloro-5-nitro-2-picoline was transformed to 5-nitro-2-picoline in 25% yield (*3*). The applications of these two methods are summarized in Table VIII-5 (p. 501).

Alkyl 5-nitro-2-pyridinemalonic esters have been converted to 2-alkyl-5-nitropyridines by treatment with sulfuric acid at 110° (*65*).

2. Properties

The nitropyridines are usually colorless to light yellow crystalline solids. They are, for the most part, low melting substances which undergo vacuum and steam distillation. Well-defined salts have been reported with various acids; 3,5-dinitropyridine, however, is only feebly basic and forms easily hydrolyzed salts (*158*). The properties of the nitropyridines are summarized in Table VIII-6 (pp. 502 ff.).

3. Reactions

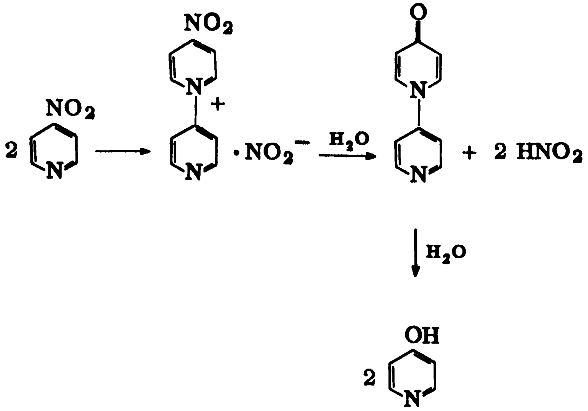
Like nitrobenzene, the nitropyridines and their substitution products are readily reduced to amines by chemical or catalytic methods. This reaction is discussed in Chapter IX (*cf.* also Table IX-6). 3-Nitropyridine closely resembles nitrobenzene in its chemical properties; its isomers, however, more nearly parallel the behavior of *o*- and *p*-dinitrobenzene. Thus, 2- and 4-nitro substituents are replaced readily by nucleophilic reagents. Katada (*97*) has compared the reactivity of these two isomers and found the 4-nitro compound to be more labile; the results are summarized in Table VIII-7 (p. 507).

a. Replacement of Nitro Groups

The replacement reactions of alkoxy-2-nitropyridines have been studied by den Hertog (*78,81*). 3,5-Diethoxy-2,6-dinitropyridine undergoes replacement of both nitro groups by bromine, with no apparent ether cleavage, on treatment with hydrobromic acid at 100°. A similar reaction occurs with 3-ethoxy-2-nitropyridine. In contrast, 2-bromo-3-ethoxy-6-nitropyridine yields 3-amino-2-bromo-6-nitropyridine by reaction with ammonia, accompanied by lesser amounts of 2-amino-3-ethoxy-6-nitropyridine. The nitro group seems to resist attack by this reagent even at higher temperatures, where 2,3-diamino-6-nitropyridine is the principal product. Similarly, the formation of 3-amino-2-nitropyridine from 3-ethoxy-2-

nitropyridine and ammonia at 150° lends support to the findings of Katada (*97*).

The exceptional lability of 4-nitropyridine is demonstrated in the findings of den Hertog (*73*). This substance behaves much like 4-chloropyridine and 4-pyridinesulfonic acid in undergoing a bimolecular displacement reaction (VIII-11).



(VIII-11)

The conversion of 4-nitropyridine to 4-pyridinol by reaction with water occurs both by direct hydrolysis and by intermediate formation of 1-(4-pyridyl)-4(1*H*)-pyridone (*73*).

The replacement reactions of nitropyridines are summarized in Table VIII-8 (pp. 508 ff.).

4-Nitropyridine 1-oxide and derivatives react with acidic and basic reagents to give numerous products; they have proved most useful intermediates for the synthesis of 4-substituted pyridines (see Chapter IV). The 1-oxides are somewhat more reactive than the corresponding 4-nitropyridines.

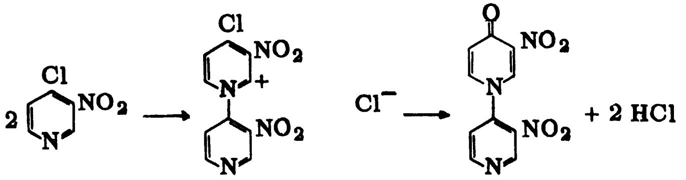
b. Activation of Substituents by Nitro Groups

Ortho and para halonitropyridines generally display an enhanced reactivity which leads to ready replacement of the halogen atom (*cf.* Chapter VI, pp. 345 ff.). Thus, 4-chloro-3-nitropyridine is hydrolyzed to the 4-pyridinol by warm water (*105*), and 4-chloro-3,5-dinitropyridine by atmospheric moisture (*152*). In the case of halo-2- and 4-nitropyridines, however, the nitro group is attacked instead.

2-Halopyridines possessing electron-attracting groups in the 3 and 5 positions are especially prone to attack by alkoxides. Mariella and co-workers (*124*) have noted the formation of an intense purple color by reaction of base with 2-chloro-3-cyano-6-methyl-5-nitropyridine and with 2-chloro-4,6-dimethyl-3,5-dinitropyridine. They considered this color to arise by formation of quinone intermediates.

Mangini (*111,113,122*) has compared the reactivity of 2-chloro-5-nitropyridine with 2,4-dinitrochlorobenzene and concluded that the latter is somewhat more reactive. On the basis of activation energy measurements, Bishop (*8*) concluded that the various nitrochloropyridines are less reactive than the dinitrochlorobenzene, in agreement with the foregoing findings. The relative order of activities would appear to be 2,4-dinitrochlorobenzene > 4-chloro-3-nitropyridine > 2-chloro-5-nitropyridine > 2-chloro-3-nitropyridine. The results are summarized in Table VIII-9 (p. 511).

4-Chloro-3-nitropyridine possesses exceptional reactivity and liberates chloride slowly in ethanolic solution. This may be the result of a self-condensation reaction (VIII-11a).



(VIII-11a)

Groups other than halogen also seem to be activated by nitro substituents. 4-Amino-3-nitropyridine and 4-amino-3,5-dinitropyridine, for example, eliminate ammonia readily by treatment with alkali (*105,112*). A nearly theoretical yield of 4-propylamino-3-nitropyridine has been reported from 4-methoxy-3-nitropyridine and propylamine (*199*). Potassium 5-nitro-2-pyridinesulfonate undergoes a similar replacement of the sulfonate group with a number of nucleophilic reagents (*121*).

Taylor and Crovetti (*194a*) have described an interesting reaction in which 4-nitro-3-picoline 1-oxide undergoes oxidative coupling to 3,3′-ethylenebis(4-nitropyridine) 1,1′-dioxide.

c. *Bimolecular Reduction of Nitro Groups*

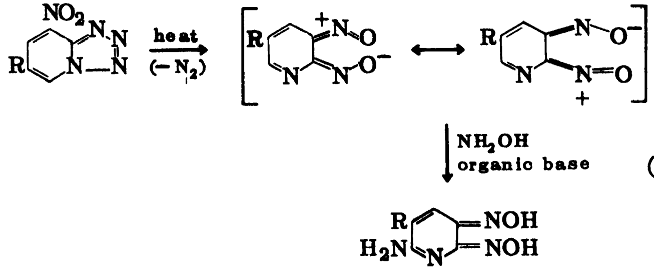
Nitropyridines and their 1-oxides show a marked tendency towards bimolecular reduction leading to azo, azoxy, and hydrazo compounds. Ochiai and Katada (*142*) have reported the formation of 4,4′-azodipyridine 1,1′-dioxide from 4-nitropyridine and ethanolic ammonia or benzylamine. Den Hertog (*74,75*) noted the occurrence of a similar process with aqueous alkali which, however, was repressed in the presence of hydrogen peroxide. The reduction reactions of 4-nitropyridine 1-oxides are summarized in Table VIII-10 (pp. 512 f.), other reactions in Table VIII-11 (pp. 513 ff.).

B. NITROSOPYRIDINES

1. Preparation

Kirpal and Reiter (*104*) synthesized 3-nitrosopyridine from the nitro compound by reduction and subsequent oxidation of the intermediate 3-hydroxylaminopyridine. 2,6-Diaminopyridine, 2-amino-6-hydroxypyridine, and 2,-6-dihydroxypyridine are nitrosated readily with nitrous acid to yield the 3-nitroso compounds (*60,196*).

Boyer and Shoen (*11*) have described the thermal decomposition of 7-nitropyrido[1,2-d]tetrazole leading to the interesting 2,3-ψ-dinitrosopyridine. Reduction with hydroxylamine and organic base leads to a dioxime (VIII-11b).

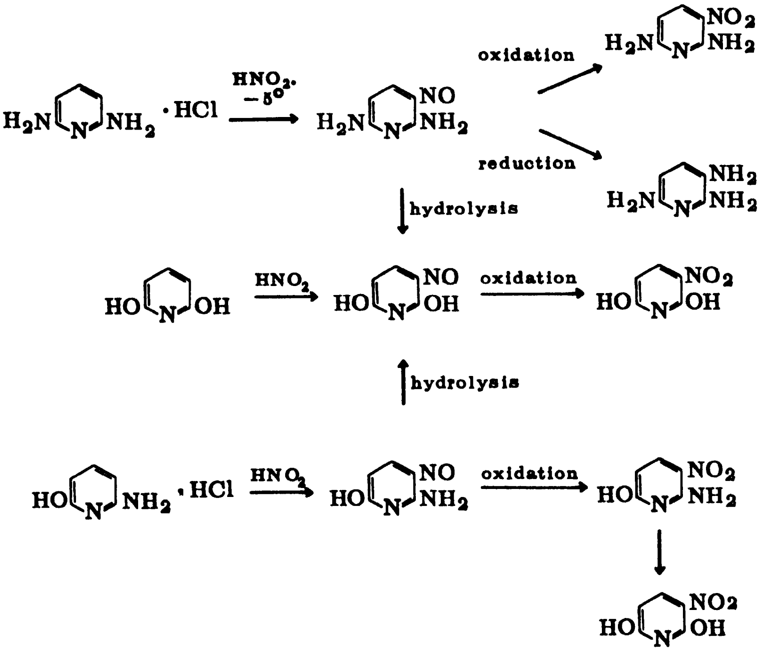


(VIII-11b)

2. Properties and Reactions

3-Nitrosopyridine is a colorless solid, m.p. 94°, which forms a green melt and yields light green solutions in water and organic solvents. It is a strong oxidizing agent and liberates iodine from iodide solutions. A deep blue color results with diphenylamine in concentrated acid.

Diaminonitroso- and aminohydroxynitrosopyridines undergo hydrolysis of the amino groups under mild conditions. The nitroso functions are oxidized to nitro with hydrogen peroxide. 2,6-Diamino-3-nitrosopyridine has been reduced to the triamine (*213*). These transformations are shown in equation VIII-12.



(VIII-12)

C. HYDROXYLAMINOPYRIDINES

3-Hydroxylaminopyridine has been prepared by reduction of 3-nitropyridine. It reduces Fehling's solution and Tollens' reagent and undergoes ready oxidation in air to the nitroso compound. Bichromate oxidation also leads to the nitroso compound, and is accompanied by the formation of 3,3′-azoxydipyridine (*104*).

Catalytic reduction of 2-nitropyridine affords 2-hydroxylaminopyridine in poor yield (*131*). Similar treatment of ethyl 2-methyl-

5-nitronicotinate yields the corresponding hydroxylamine in moderate amounts (*55*).

Nitrosopyridines and hydroxylaminopyridines are summarized in Table VIII-12 (p. 516).

D. AZOPYRIDINES

1. Preparation

The preparation of azopyridines is accomplished readily by a variety of methods. In general, 3-azopyridines are formed by reactions applicable to the benzene series. 2- and 4-Azopyridines sometimes require special methods for their formation.

a. By Coupling Reactions from Pyridinediazonium Salts

Sodium 2-pyridinediazotate undergoes coupling with resorcinol, α-naphthol, and 2,6-diaminopyridine to yield azo compounds. A similar reaction occurs between diazotized 4-aminopyridine and β-naphthol (*147*). Dimethylaniline, however, does not react with the former diazonium salt under these conditions nor can it be coupled with 2- or 4-aminopyridine after diazotization with nitrosylsulfuric acid, amyl nitrite, or nitric acid–potassium metabisulfite (*25,27,48, 54, 102,111*).

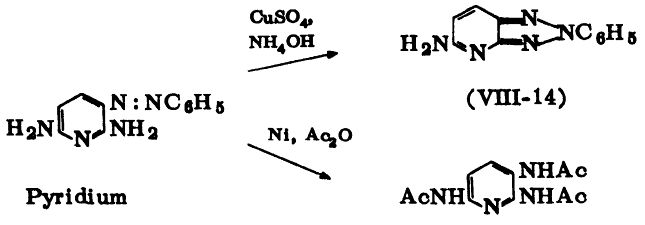
3-Aminopyridines exhibit normal behavior in coupling reactions and form azo compounds with resorcinol, dimethylaniline, β-naphthol, and other agents (*129,164,170,182,183,185,215*).

b. From Pyridine Derivatives as Coupling Components

Diazotized aromatic amines undergo coupling reactions with certain aminopyridines. 2,6-Diaminopyridine and benzenediazonium chloride form 2,6-diamino-3-phenylazopyridine (Pyridium) (VIII-13) in acid solution. An additional coupling to give 2,6-diamino-3,5-bis(phenylazo)pyridine also occurs, especially in the presence of excess diazotized aniline (*28,29,208*).

Ostromislensky (*209*) first noted the formation of a side product in the reaction between benzenediazonium chloride and 2,6-diaminopyridine. Subsequent work showed its formation from 2,4-diaminopyridine, which occurred as an impurity in the diamine employed (*39,150*).

The structure of Pyridium (2,6-diamino-3-phenylazopyridine) was demonstrated by conversion to a triazole (VIII-14) (*24*) and by catalytic reduction in acetic anhydride to 2,3,6-triacetamidopyridine (VIII-15) (*31*).



(VIII-13)

(VIII-14)

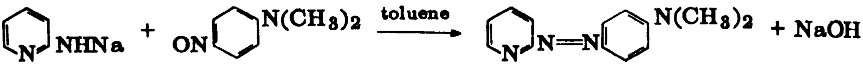
(VIII-15)

Citrazinic acid undergoes coupling with diazotized sulfapyridine (*232*).

3,5-Diaminopyridine couples with diazonium compounds in the 2 position (*228*).

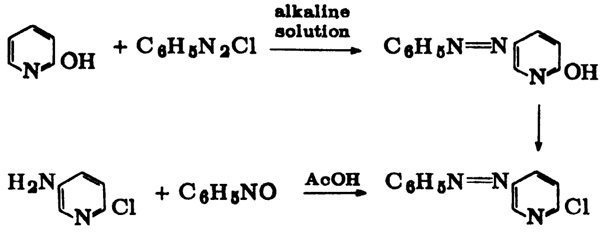
c. *By Condensation Methods*

Faessinger and Brown have investigated a number of approaches to the synthesis of pyridine analogs of *p*-dimethylaminoazobenzene ("butter yellow") (*54*). They reported that *p*-nitrosodimethylaniline failed to condense with 2-aminopyridine by heating with powdered sodium hydroxide, a process which has found successful application in the benzene series (*125*). The sodium salt of 2-aminopyridine, however, reacts with *p*-nitrosodimethylaniline to yield the desired 2-(*p*-dimethylaminophenylazo)pyridine (VIII-16). This compound is also produced by interaction of disodium-*p*-nitrodimethylaniline and 2-aminopyridine. An analogous reaction occurs with 4-aminopyridine.



(VIII-16)

Anomalous results have been obtained in the reaction between 3-aminopyridine and *p*-nitrosodimethylaniline; 4,4′-azobis(*N,N*-dimethylaniline) is formed in place of the expected 3-(*p*-dimethylaminophenyl)azopyridine. An analogous reaction between 3-amino-6-chloropyridine and nitrosobenzene, however, proceeds normally. The substance obtained in this case is identical to that formed by the reaction of 2-pyridinol and benzenediazonium chloride, followed by chlorination (VIII-17) (*128*).



(VIII-17)

d. *By Oxidation of Aminopyridines*

Kirpal and Reiter (*103*) first effected the oxidation of 2-aminopyridine to 2,2′-azodipyridine. Subsequently, Kirpal and Bohm (*102*) reported the formation of two isomeric 2,2′-azodipyridines, m.p. 81° and 87°, from this reaction; the lower melting substance, however, was shown to be a chlorinated derivative (*100*).

Numerous other azodipyridines have been prepared by this oxidation method. Thus, 3-aminopyridine yields 3,3′-azodipyridine; this substance is identical to that obtained by reduction of the nitro compound (*102*). 3-Aminopyridine periodide undergoes conversion to the same azo compound by treatment with alkali; this is a modification of the hypochlorite oxidation process employed previously (*173*).

The oxidation of aminopyridines to azopyridines is summarized in Table VIII-13 (p. 517).

e. *By Reduction Methods*

2,2′-Azodipyridine results on reduction of the nitropyridine with arsenous oxide in alkaline solution (*102,118*); under similar conditions, however, 3-nitropyridine undergoes conversion to the azoxy compound (*58*). Stannite solutions have also yielded azodipyridines

(*140*). The reduction of nitropyridines to azopyridines is summarized in Table VIII-14 (pp. 517 f.).

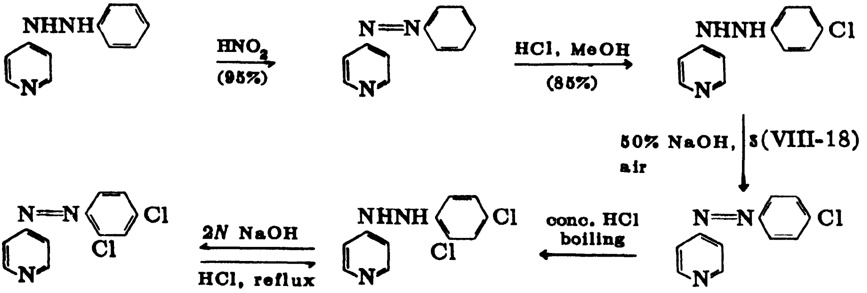
The reduction of 3,3′-azoxydipyridine with zinc and alkali to the azo compound proceeds quantitatively (*58,83*). Reduction with iron, however, is incomplete (*58*). 4,4′-Azoxydipyridine 1,1′-dioxide is reduced effectively with zinc and acetic acid to 4,4′-azodipyridine 1,1′-dioxide (*132*).

f. From Pyridine and Nitrogen Dioxide

Den Hertog (*83*) attempted the nitration of pyridine with nitrogen dioxide at elevated temperatures with a vanadium catalyst. The product of this reaction, however, was 3,3′-azodipyridine in low yield.

g. From Hydrazopyridines

Hydrazopyridines undergo ready oxidation to the corresponding azo compounds. Koenigs (*107*) has reported an interesting series of reactions involving oxidation of *N*-phenyl-*N*′-(4-pyridyl)hydrazine (VIII-18). Similar transformations may be effected with hydrobromic acid, leading to brominated azo and hydrazo derivatives. Other hydrazopyridines are converted easily to the corresponding azo compounds by air or dilute nitric acid oxidation. This method of preparing azopyridines is summarized in Table VIII-15 (pp. 518 f.).



2. Properties

The azopyridines generally are highly colored, well-crystallized solids which cover a wide melting point range. Salts with organic and inorganic acids have been reported in some cases.

Dipole moment measurements on 2,2′-azodipyridine indicate that this substance probably exists in the *trans* form (*118*). LeFevre and Worth have reported a partial conversion to the *cis* modification with sunlight. Campbell (*21*) effected this conversion with mercury vapor irradiation; the *cis*, m.p. 87°, and *trans*, m.p. 83°, isomers can be separated with silica gel. The reverse transformation is carried out by repeated heating and cooling. *cis*- and *trans*-3,3′-Azodipyridine exhibit a similar behavior.

The properties of azopyridines are summarized in Table VIII-16 (pp. 520 ff.). (*Cf.* also Chapter IX, Tables IX-44 through IX-48.)

3. Reactions

Azopyridines can be reduced easily to hydrazo and amino compounds. Thus, reduction of 2,2′-azodipyridine with stannous chloride yields the hydrazo compound (*103*), and catalytic reduction of 2,6-diamino-3-phenylazopyridine in acetic anhydride affords 2,3,6-triacetamidopyridine (*31*). The latter azo compound undergoes dehydrogenation with the formation of a triazole (VIII-14) (*24*). Faessinger and Brown (*54a*) have reported that 2-(*p*-dimethylaminophenylazo)pyridine 1-oxide undergoes deoxygenation with lithium aluminum hydride without affecting the azo linkage.

The reaction of 2-phenylazopyridine with phenylmagnesium bromide and benzylmagnesium bromide proceeds to give *N,N*-diphenyl-*N*′-2-pyridylhydrazine and *N*-benzyl-*N*-phenyl-*N*′-2-pyridylhydrazine, respectively (*47*). 2,2′-Azodipyridine reacts analogously (*48a*).

4. Pharmacology

Pyridium (VIII-13) is perhaps the best known of the azopyridines and continues to enjoy use as a medicinal agent even though other azo compounds have become obsolete. Although introduced as a urinary antiseptic (*206*), it is presently used principally as an analgetic agent in such disorders as cystitis, pyelitis, and prostatitis. The monoacetyl derivative has been patented as an antineuralgic agent (*230*).

Pyridium, like its analogs, possesses an antibacterial effect against gram positive and gram negative organisms; it imparts a red color to urine. Several patents have been issued during recent years for antibacterial agents of this general type (*231,234,236*).

Brown and associates (*16*) have shown that a number of pyridine analogs of *p*-dimethylaminoazobenzene ("butter yellow") are carcinogenic in varying degrees.

E. AZOXYPYRIDINES

Azoxpyridines are formed by the reduction of nitropyridines with arsenites (*18,58*). 4,4′-Azoxydipyridine 1,1′-dioxide and related compounds are obtained from 4-nitropyridine 1-oxide by reduction with zinc in neutral or acid solution (*132,141,143*). 2-Phenylazopyridine undergoes oxidation with perbenzoic acid to 2-phenylazopyridine α,1-dioxide. The reaction proceeds through the azopyridine 1-oxide to the azoxy compound (*48*).

Azoxypyridines undergo smooth reduction to the azo compounds, and may be oxidized with per-acids to either mono- or di-*N*-oxides. They are summarized in Table VIII-17 (pp. 525 f.).

F. HYDRAZINOPYRIDINES

2- and 4-Hydrazinopyridines are readily available by a number of methods which employ nitramino, halo, and other substituted pyridines as starting materials. Methods for the preparation of the 3-hydrazino isomers do not include replacement reactions, which are peculiar to the 2 and 4 positions. In this instance the reduction of diazonium salts is applicable.

The direct hydrazination of pyridine has recently been accomplished by treatment with sodium hydrazide. The reaction, which yields 2-hydrazinopyridine, is analogous to the amination reaction with sodamide. Substituted 2-hydrazinopyridines are also available by this route (*98b*).

1. Preparation

a. From Halopyridines

2-Halopyridines react much more readily with hydrazine than with ammonia, giving 2-hydrazinopyridines in high yields (*56,61*).

The activated halogen of 2-chloro-5-nitropyridine and related compounds undergoes even more ready substitution. The doubly activated 4-chloro-3,5-dinitropyridine reacts with hydrazine at room temperature to afford 3,5-dinitro-4-hydrazinopyridine (*158*).

Baumgarten and Su (2) have noted the successful reaction between hydrazine and 6-chloro-5-nitro-2-picoline; they found, however, that an analogous reaction with 6-chloro-3-nitro-2-picoline is accompanied by reduction which renders the halogen inert; the normal replacement product, 6-hydrazino-3-nitro-2-picoline, formed only in very low yield.

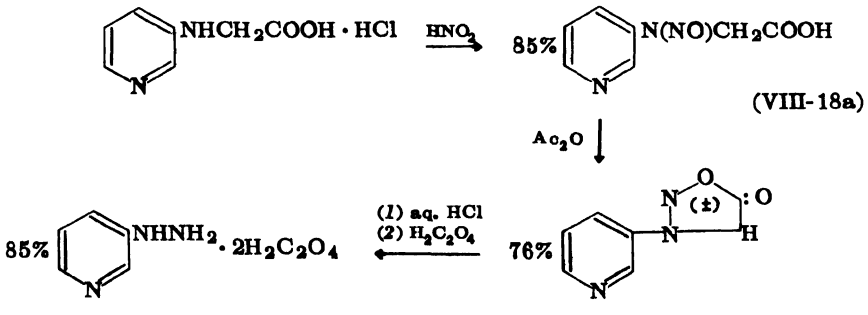
b. From Pyridinesulfonic Acids

Pyridine-2-sulfonic acid and 5-nitro-2-pyridinesulfonic acid react readily with hydrazine to give the respective hydrazinopyridines (*121*).

c. From Nitraminopyridines

Nitraminopyridines have proved useful intermediates for the synthesis of hydrazinopyridines. Thus, Chichibabin (*34,41*) reduced 2- and 3-nitraminopyridines by conventional means. Koenigs (*112*) has prepared 4-hydrazinopyridine by a similar process; 2- and 3-methylnitraminopyridines also undergo this conversion (*37,159*).

Tien and Hunsberger (*195*) have described an interesting conversion of *N*-(3-pyridyl)glycine to 3-hydrazinopyridine. Nitrosation of the amino acid gives the *N*-nitroso compound, which undergoes easy transformation into the sydnone; this in turn yields the hydrazino compound by acid cleavage (VIII-18a).



(VIII-18a)

d. From Pyridinediazonium Salts

3-Aminopyridine and 6-chloro-3-aminopyridine have been diazotized and reduced to the corresponding hydrazine derivatives (*153,164,181a,195,207*).

2. Properties

The simpler hydrazinopyridines are oils or low melting solids which are unstable in air. They form well-defined salts and give characteristic reactions with Fehling solution and ammonical silver nitrate. The hydrazinopyridines form hydrazones and pyrazolones in typical fashion (*47,127,221*). Reaction with phenyl isothiocyanate has been reported also (*123*).

Coordination complexes are formed with ferrous and ferric iron and with other metals (*53,116*).

The hydrazinopyridines are summarized in Table VIII-18 (pp. 527 ff.).

3. Reactions

a. Replacement Reactions

The hydrazino group of 2-hydrazinopyridines undergoes ready replacement by hydrogen. Thus, Räth has converted 2-hydrazino-5-nitropyridine to 3-nitropyridine by oxidation with copper sulfate in an acid medium (*164,229*). Hydrazinonitropicolines undergo a similar transformation in 30–40% yields (*2,15*); 4-hydrazinopyridines behave analogously (*86*). (*Cf.* Table VIII-4, p. 501.)

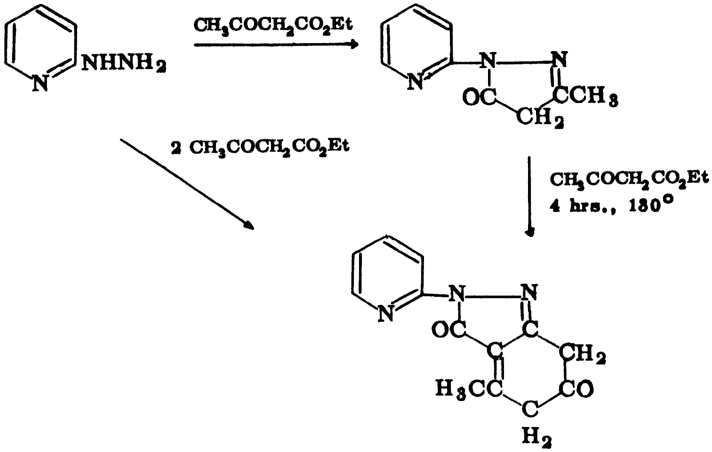
2-Nitro-4-hydrazinopyridine undergoes decomposition with evolution of nitrogen on warming with alkali (*105*).

b. Condensation Reactions

Acetoacetic ester reacts with 2-hydrazinopyridine to form the pyrazolone in quantitative yield. An additional reaction ensues in the presence of excess ester (VIII-19) (*56,224*).

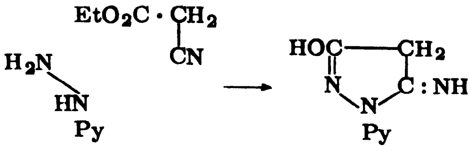
Levulinic ester reacts in an analogous fashion, the product being a pyridazine derivative (*225*).

Other examples of this general type are found in the reaction of malonic acid derivatives with hydrazinopyridines. In this connection Weissberger (*200,201*) has shown that ethyl malonate monoimido ester and ethyl cyanoacetate react with 2-hydrazinopyridine to form pyrazolones. 2-Hydrazinopyridine apparently reacts differently from either of the other isomers, and two alternative routes are evident (VIII-20). 2-Hydrazinopyridine yields a product which produces a dye with *p*-nitrosodimethylaniline, while the other

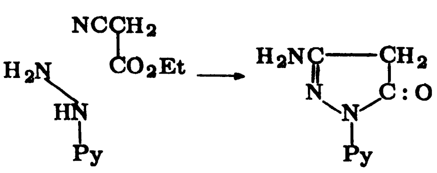


(VIII-19)

isomers do not. Experience among similar compounds in the benzene series has revealed that Type 1 products alone undergo this color reaction.



Type 1. 2-Hydrazinopyridine

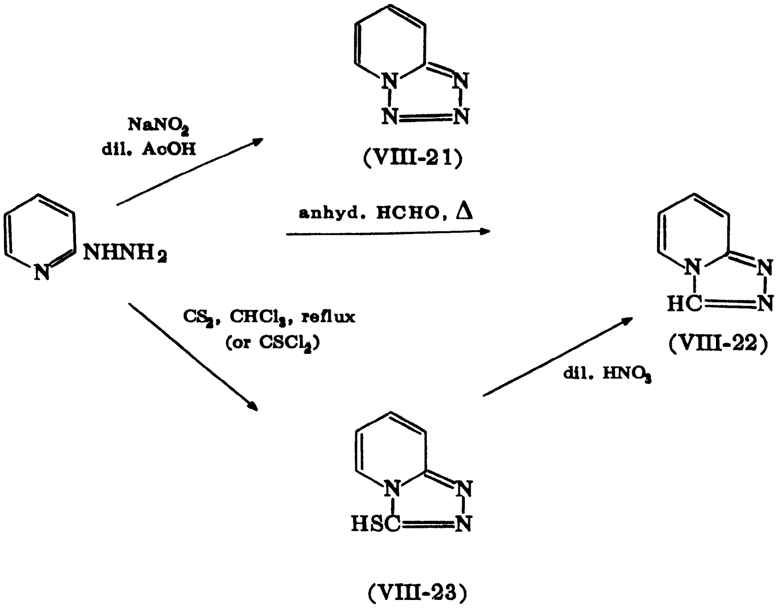


Type 2. 3- and 4-Hydrazinopyridines

(VIII-20)

c. Formation of Condensed Ring Systems

Bicyclic compounds form readily from 2-hydrazinopyridine with participation of the pyridine nitrogen. With nitrous acid the product is a pyridotetrazole (VIII-21) (*56,121*). Treatment with formaldehyde yields a triazole (VIII-22) (*56*), while carbon disulfide or thiophosgene forms a mercaptotriazole (VIII-23) (*193*), which is identical with that produced by Mills and Schindler (*127*) from trithiocarbonic acid derivatives. Compounds of this type are summarized in Table VIII-19 (pp. 530 ff.).



2-Chloro-5-hydrazinopyridine participates in the Fischer indole synthesis (*184*).

G. HYDRAZOPYRIDINES

1. Preparation

Hydrazopyridines are generally available by reduction of the corresponding azo compounds, and by reaction of 2- and 4-chloropyridines with substituted hydrazines. Kirpal and Reiter (*103*) thus prepared 2,2′-hydrazodipyridine by stannous chloride reduction of the azo compound. In another case 3,3′-hydrazodipyridine was obtained by zinc-alkali reduction of 3,3′-azodipyridine (*58*). This reduction process has not been reported for 4-nitropyridine, but 4-

nitropyridine 1-oxide is stated to yield 4,4-hydrazodipyridine 1,1'-dioxide (*132,141*).

The preparation of 2,2'-hydrazodipyridine from 2-chloropyridine and 2-hydrazinopyridine has been described (*223*).

2. Properties and Reactions

Hydrazopyridines are oxidized readily, especially in alkaline solution, to the corresponding azo compounds (*39,107,132*). 2,2'-Hydrazodi-(3,5-dinitropyridine) has been converted to 3,5-dinitropyridine by reaction with silver acetate; concurrent formation of the related azo compound seems to occur (*158*).

Räth (*164*) has attempted the benzidine rearrangement of 3,3'-hydrazodipyridine, without apparent success.

H. PYRIDYL AZIDES

Boyer and Kruger (*9a*) have prepared 3-nitro-4-pyridyl azide from the nitrochloro compound by reaction with sodium azide. The compound decomposes at the melting point, but is apparently stable at lower temperatures.

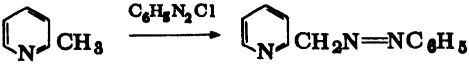
I. SIDE-CHAIN DERIVATIVES

Various side-chain derivatives of the types under discussion have been reported in the literature. Their synthesis proceeds from certain reactive pyridine compounds such as 2- and 4-vinylpyridines, pyridine aldehydes, and 2-picoline. Side-chain nitration has been reported to occur in certain substituted pyridines.

2-Vinylpyridine and related compounds add nitrous acid to form the corresponding 2- and 4-(2-nitroethyl)pyridines (*214*). A similar reaction with hydrazoic acid yields β-2-pyridylethyl azide (*9*).

2-Vinylpyridine, 4-vinylpyridine, and 6-methyl-2-vinylpyridine react with nitroalkanes with basic catalysis; the products are 1-pyridyl-3-nitro-2-substituted propanes (*163a*).

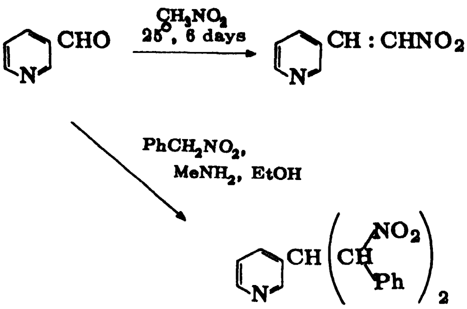
2- and 4-Picolines are sufficiently reactive to form side-chain azo compounds with *p*-nitrobenzenediazonium chloride (VIII-24); this



(VIII-24)

reaction has been suggested as a method for determining the reactivity of hydrogen atoms (*238*).

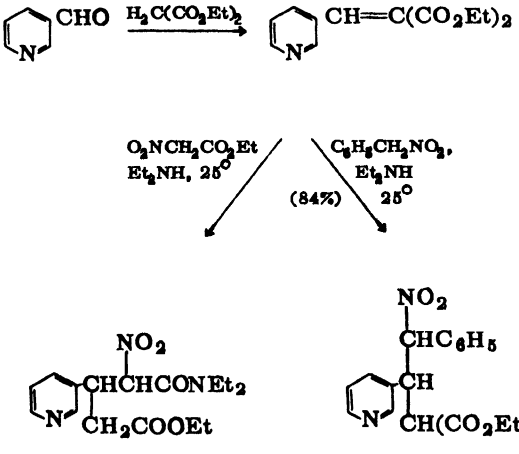
Pyridine aldehydes condense with compounds containing activated methylene groups to form a number of different products. With nitromethane, the reaction product of nicotinaldehyde is a nitrostyrene analog, while with phenylnitromethane a dinitro derivative results (VIII-25) (*205*).



(VIII-25)

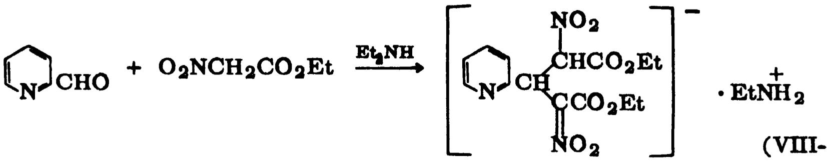
The reaction of pyridine 2- and 4-aldehydes with nitromethane, under controlled conditions, proceeds to give the corresponding nitro alcohols, which in turn have been reduced to the amino alcohols (*190*).

Nicotinaldehyde condenses readily with malonic ester, and this product undergoes additional reactions with phenylnitromethane and ethyl nitroacetate (VIII-26).



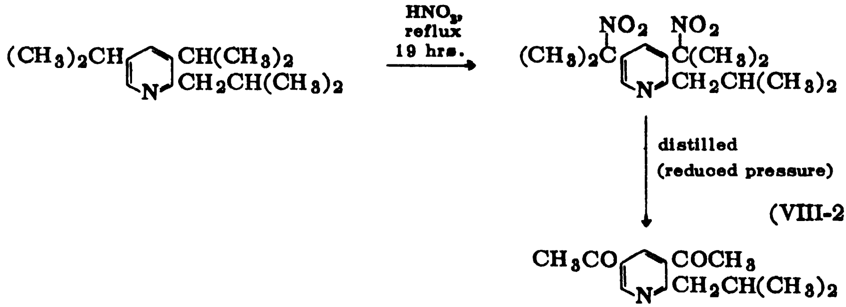
(VIII-26)

Picolinaldehyde reacts with 2 moles of nitroacetic ester in the presence of diethylamine to yield the diethylammonium salt of pyridyldinitroglutaric ester (VIII-27) (*51,52*).



(VIII-27)

Oparina has demonstrated the ability of certain substituted pyridines to undergo side-chain nitration (*149*). The product of this reaction underwent ready elimination of the nitro groups to form ketonic compounds (VIII-28).

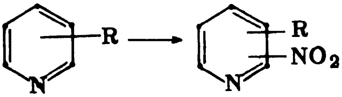


(VIII-28)

The side-chain compounds are summarized in Table VIII-20 (pp. 536 ff.).

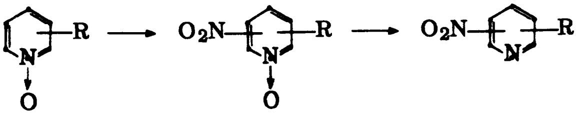
J. TABLES

TABLE VIII-1. Nitration of Homologous Pyridine Bases



Starting material	Conditions	Product (yield)	Ref.
Pyridine	KNO_3, fuming HNO_3 (330°)	3-$PyNO_2$ (15%)	57
	KNO_3, fuming HNO_3, 100% H_2SO_4 (290-300°)	3-$PyNO_2$ (13%)	58
	KNO_3, fuming HNO_3, 100% H_2SO_4, + 0.1% Fe wire (290-300°)	3-$PyNO_2$ (22%)	104
	KNO_3-$NaNO_3$, 100% H_2SO_4 (300°)	2-$PyNO_2$ (0.5%) 3-$PyNO_2$ (4.5%)	
	KNO_3-$NaNO_3$, 100% H_2SO_4 (370°)	2-$PyNO_2$ (2%) 3-$PyNO_2$ (4%)	83
	KNO_3-$NaNO_3$, 100% H_2SO_4 (450°)	2-$PyNO_2$ (2.5%)	
	NO_2, CO_2 (115-120°)	3-$PyNO_2$ (7-10%)	172
2-Picoline	KNO_3, fuming H_2SO_4 (160°)	5-nitro-2-picoline (3.6%)	157
2,6-Lutidine	KNO_3, fuming H_2SO_4 (100°)	3-nitro-2,6-lutidine (66%)	157
s-Collidine	KNO_3, H_2SO_4 (100°)	3-nitro-*s*-collidine (90%)	157

TABLE VIII-2. Nitration and Deoxygenation of Pyridine 1-Oxides



Starting material	Nitrating conditions	Nitration product (yield)	Deoxygenation conditions	Product (yield)	Ref.
Pyridine 1-oxide	conc. H_2SO_4, fuming HNO_3 (130°)	4-nitropyridine 1-oxide (72%)	KNO_3, conc. H_2SO_4 (165°)	4-nitropyridine (poor)	69,96,132, 133,136, 137,147, 148
	conc. H_2SO_4, conc. HNO_3 (160°)	4-nitropyridine 1-oxide (43%) 4-nitropyridine (27%) 2-nitropyridine (7.6%)	PCl_3, 70–80°	4-nitropyridine	132
	fuming H_2SO_4, fuming HNO_3 (100°)	4-nitropyridine 1-oxide (60–90%)	PCl_3, $CHCl_3$ 70–80°	4-nitropyridine (79%)	132
	conc. H_2SO_4, fuming HNO_3 (90°)	4-nitropyridine 1-oxide (85–90%)			84
2-Picoline 1-oxide	conc. H_2SO_4, fuming HNO_3 (80°)	4-nitro-2-picoline 1-oxide (85–90%)			80
3-Picoline 1-oxide	conc. H_2SO_4, fuming HNO_3 (100°)	4-nitro-3-picoline 1-oxide (76%)			194
	H_2SO_4, KNO_3 (100°)	4-nitro-3-picoline 1-oxide (35%)			80

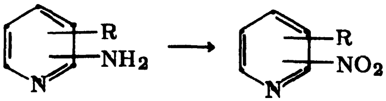
(continued)

TABLE VIII-2. Nitration and Deoxygenation of Pyridine 1-Oxides (*continued*)

Starting material	Nitrating conditions	Nitration product (yield)	Deoxygenation conditions	Product (yield)	Ref.
2,6-Lutidine 1-oxide	H_2SO_4, KNO_3	4-nitro-2,6-lutidine 1-oxide			134
2,2′-Bipyridine-1,1′-oxide		4,4′-dinitro-2,2′-bipyridine-1,1′-oxide	PCl_3, $CHCl_3$	4,4′-dinitro-2,2′-bipyridine	119a
2-Bromopyridine 1-oxide	H_2SO_4, fuming HNO_3 (90°)	2-bromo-4-nitropyridine 1-oxide			80
3-Bromopyridine 1-oxide		3-bromo-4-nitropyridine 1-oxide (91%)			94
	conc. H_2SO_4, fuming HNO_3 (90°)	3-bromo-4-nitropyridine 1-oxide (40%)			84
2,6-Dibromopyridine 1-oxide	conc. H_2SO_4, conc. HNO_3	2,6-dibromo-4-nitropyridine 1-oxide (80%)			53a
3,5-Dibromopyridine 1-oxide	H_2SO_4, fuming HNO_3	3,5-dibromo-4-nitropyridine 1-oxide (90–95%)			76
2-Ethoxypyridine 1-oxide	fuming HNO_3 (90°)	2-ethoxy-4-nitropyridine 1-oxide (10–15%)			80
3-Ethoxypyridine 1-oxide	H_2SO_4, fuming HNO_3 (85°)	3-ethoxy-4-nitropyridine 1-oxide (70–80%)			80
3,5-Diethoxypyridine 1-oxide	KNO_3, H_2SO_4 (0°)	3,5-diethoxy-2-nitropyridine 1-oxide (90–100%)			76
	H_2SO_4, fuming HNO_3 (85°)	3,5-diethoxy-2-nitropyridine (90–95%)			76

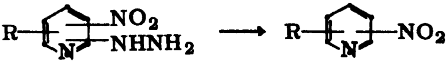
2-Pyridinol 1-oxide	AcOH, HNO_3 (cooling)	5-nitro-2-pyridinol (67%)			87,119
4-Pyridinol 1-oxide	AcOH, HNO_3	3,5-dinitro-4-pyridinol 1-oxide (80%)	PCl_3, AcOEt, (20°)	3,5-dinitro-4-pyridinol	72,135
	Ac_2O, HNO_3, (75°)	3-nitro-4-pyridinol 1-oxide (90%)			72
2-Methyl-4-pyridinol 1-oxide	AcOH, HNO_3, (70°)	2-methyl-3,5-dinitro-4-pyridinol 1-oxide (67%)			179
	AcOH, HNO_3, (65–70°)	2-methyl-3-nitro-4-pyridinol 1-oxide (44.1%)			179
		2-methyl-5-nitro-4-pyridinol 1-oxide (14.7%)			179
2-Methoxypyridine 1-oxide	H_2SO_4, fuming HNO_3	2-methoxy-4-nitropyridine 1-oxide			87
3-Methoxypyridine 1-oxide	H_2SO_4, fuming HNO_3	3-methoxy-4-nitropyridine 1-oxide			87
5-Bromo-3-methoxypyridine 1-oxide	H_2SO_4, KNO_3 (30–35°)	5-bromo-3-methoxy-2-nitropyridine 1-oxide			87
3,5-Dimethoxypyridine 1-oxide	H_2SO_4, KNO_3 (0°)	3,5-dimethoxy-2-nitropyridine 1-oxide			87

TABLE VIII-3. Preparation of Nitropyridines by Oxidation of Aminopyridines



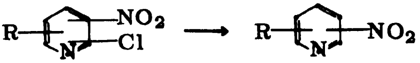
Aminopyridine	Oxidation conditions	Product (yield)	Ref.
2-PyNH$_2$	$(NH_4)_2S_2O_8$, (25°)	2-PyNO$_2$ (30%)	101
	H_2O_2, fuming H_2SO_4	2-PyNO$_2$ (75%)	102
3-PyNH$_2$	H_2O_2, fuming H_2SO_4 (25°)	3-PyNO$_2$ (38%)	173
4-PyNH$_2$	H_2O_2, fuming H_2SO_4	4-PyNO$_2$ (80%)	102
2-Amino-3-picoline	H_2O_2, H_2SO_4 (25°)	2-nitro-3-picoline (60–68%)	203
2-Amino-4-picoline	H_2O_2, H_2SO_4 (25°)	2-nitro-4-picoline (68%)	203
6-Amino-3-picoline	H_2O_2, H_2SO_4 (25°)	6-nitro-3-picoline (30%)	203
6-Amino-2-picoline	H_2O_2, H_2SO_4(25°)	6-nitro-2-picoline (60–68%)	203
3-Amino-2-picoline	Cupro-cupri sulfite, HNO_3	3-nitro-2-picoline (15%)	2
4-Amino-2-picoline	H_2O_2, H_2SO_4 (10–20°)	4-nitro-2-picoline (55%)	15
4-Amino-3-picoline	H_2O_2, fuming H_2SO_4 (20–30°)	4-nitro-3-picoline (82%)	15
2-Amino-5-bromopyridine	H_2O_2, H_2SO_4 (0–5°)	2-nitro-5-bromopyridine (85%)	177
	H_2O_2, H_2SO_4 (0–5°)	2-nitro-5-bromopyridine (60%)	18
	Caro's acid (10–15°)	2-nitro-5-bromopyridine (37%)	1
	H_2O_2, H_2SO_4(16°)	2-nitro-5-bromopyridine (50–55%)	79
2-Amino-3,5-dibromopyridine	H_2O_2, H_2SO_4 (5–15°)	2-nitro-3,5-dibromopyridine	79
2-Amino-5-chloropyridine	H_2O_2, H_2SO_4 (0–5°)	2-nitro-5-chloropyridine (40%)	18
	H_2O_2, H_2SO_4 (0–5°)	2-nitro-5-chloropyridine (81%)	177

TABLE VIII-4. Conversion of Hydrazinonitropyridines to Nitropyridines



Hydrazinonitropyridine	Conditions	Product (yield)	Ref.
2-Hydrazino-5-nitropyridine	$CuSO_4$, acid	3-nitropyridine (50%)	164,210
6-Hydrazino-5-nitro-2-picoline	$CuSO_4$, dil. AcOH	5-nitro-2-picoline (43%)	2
6-Hydrazino-3-nitro-2-picoline	$CuSO_4$, dil. AcOH	3-nitro-2-picoline (20%)	3
6-Hydrazino-5-nitro-3-picoline	$CuSO_4$, dil. AcOH	5-nitro-3-picoline (53%)	15
2-Hydrazino-3,5-dinitropyridine	AgOAc, H_2O (reflux)	3,5-dinitropyridine (80%)	158
N,*N'*-Bis(3,5-dinitro-2-pyridyl)hydrazine	AgOAc, H_2O (reflux)	3,5-dinitropyridine (40%)	158

TABLE VIII-5. Conversion of Halonitropyridines to Nitropyridines



Halonitropyridine	Conditions	Product (yield)	Ref.
2-Chloro-3-nitro-4-picoline	Cu, $C_6H_5CO_2H$ (150°)	3-nitro-4-picoline (70%)	15
6-Chloro-3-nitro-2-picoline	Cu, $C_6H_5CO_2H$ (160-80°)	3-nitro-2-picoline (27-45%)	3
	NaI-H · CO_2H (100°)		3
2-Chloro-3-nitro-4-picoline	Cu, $C_6H_5CO_2H$ (150-60°) *or*	3-nitro-4-picoline (44%)	3
2-Chloro-5-nitro-4-picoline	Cu, CH_3CO_2H		
6-Chloro-5-nitro-2-picoline	Cu, $C_6H_5CO_2H$ (150°)	5-nitro-2-picoline (80%)	15
6-Chloro-5-nitro-2-picoline	Cu, $C_6H_5CO_2H$ (160-80°)	5-nitro-2-picoline (38%)	3
6-Chloro-5-nitro-2-picoline	NaI, H · CO_2H (100°)	5-nitro-2-picoline (25%)	3

TABLE VIII-6. Nitropyridines

Compound	Physical properties, derivatives	Remarks	Ref.
2-Nitropyridine	m.p. 71°; b.p. 256°; 1-oxide, m.p. 85–86°	yellow crystals, steam volatile	15a,83,101
3-Nitropyridine	m.p. 41°; b.p. 216°; B · HCl, m.p. 154°; $B_2H_2PtCl_6$, m.p. 254°; B · $HAuCl_4$, m.p. 140°; $B_2 \cdot AgNO_3$, m.p. 175–6°	colorless needles with faint odor, steam volatile	57,58,83,104, 229
4-Nitropyridine	m.p. 50°	plates	69,102,132
3,5-Dinitropyridine	m.p. 106°	colorless crystals	158
2-Nitro-3-picoline	m.p. 43–44°; 1-oxide, m.p. 110–11°	light yellow crystals	15a,203
2-Nitro-4-picoline	m.p. 61–62°; 1-oxide, m.p. 118–19°	light yellow crystals	15a,203
6-Nitro-3-picoline	m.p. 94–95°; 1-oxide, m.p. 112–13°		15a,203
6-Nitro-2-picoline	m.p. 113–14°		203
	1-oxide, m.p. 120–21		15a
3-Nitro-2-picoline	b.p. 99–100°/8 mm. b.p. 110–12°/16 mm. B · HCl, m.p. 165–67°	yellow oil	2,3
3-Nitro-4-picoline	b.p. 85°/3 mm. B · HCl, m.p. 176–77° picrate, m.p. 118°	hygroscopic yellow oil (darkens rapidly)	3,13,106

5-Nitro-3-picoline	m.p. 90–91°		15
5-Nitro-2-picoline	m.p. 107–8°; m.p. 107.5–8.5°; m.p. 112°; m.p. 110–12°; picrate, m.p. 132°	colorless flat needles	2,3,15,67,157
4-Nitro-2-picoline	m.p. 32–34°; m.p. 42–45°		15,144
3-Nitro-2,6-lutidine	m.p. 37°; b.p. 227°/738 mm.; picrate, m.p. 143°		157
6-Nitro-2,4-lutidine	1-oxide, m.p. 108-9°		15a
4-Nitro-3-picoline	m.p. 28-29°; b.p. 67-69°/1.5 mm.; picrate, m.p. 128–29°		15,89
3-Nitro-2,4,6-collidine	m.p. 38°; m.p. 35.6°; picrate, m.p. 175°; chloroplatinate, m.p. 216°; chloroaurate, m.p. 128°; methiodide, m.p. 40–41°		157,167
5-Nitro-2-ethylpyridine	picrate, m.p. 189–91°		65
5-Nitro-2-propylpyridine	b.p. 60–70°/0.005 mm.; picrate, m.p. 163–65°		65,67
5-Nitro-2-butylpyridine	picrate, m.p. 142–43°; chloroplatinate, m.p. 181–83° (dec.)		65
5-Nitro-2-*sec*-butylpyridine	picrate, m.p. 151–53°		65

(continued)

TABLE VIII-6. Nitropyridines (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
5-Nitro-2-pentylpyridine	b.p. 120–30°/2 mm.; picrate, m.p. 150–52°; chloroplatinate, m.p. 152–55° (dec.)		65
5-Nitro-2-phenethylpyridine	picrate, m.p. 113–15°		65
3-Nitro-4-styrylpyridine	m.p. 114–15°; m.p. 118°	fine yellow needles	13,140
3-Nitro-2,6-distyrylpyridine	m.p. 134° (+1 H_2O); m.p. 158°		140
5,5′-Dinitro-2,2′-bipyridine	m.p. 244–45°		23
4,4′-Dinitro-2,2′-bipyridine	m.p. 195–97°; 1,1′-dioxide, m.p. 261° (dec.)	orange needles	119a,129a
2-Bromo-5-nitropyridine	m.p. 151–52°; m.p. 137–38°		17,19,204
2-Bromo-3-nitropyridine	m.p. 125°		5,17
5-Bromo-2-nitropyridine	m.p. 149.5–50°; m.p. 148.5°		18,79
3,5-Dibromo-2-nitropyridine	m.p. 77–77.5°		79
2,5-Dibromo-3-nitropyridine	m.p. 93°; m.p. 94–95°		5,17
5-Bromo-6-chloro-3-nitro-2,4-lutidine	m.p. 83°		124
6-Chloro-3,5-dinitro-2,4-lutidine	m.p. 84°		124
4-Chloro-3,5-dinitro-2,6-lutidine	m.p. 143.5–44°		237

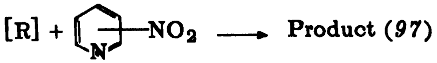
2-Bromo-5-chloro-3-nitropyridine	m.p. 75°		5
5-Bromo-2-chloro-3-nitropyridine	m.p. 68°		5
2-Chloro-3-nitropyridine	m.p. 101°		5,30,169
2-Chloro-4-nitropyridine	1-oxide, m.p. 152–53°		15a
2-Chloro-5-nitropyridine	m.p. 106°; m.p. 108–10°; m.p. 119–21°		26,162,177
5-Chloro-2-nitropyridine	m.p. 120.5–21°		18
4-Chloro-3-nitropyridine	m.p. 45°; b.p. 95°/5 mm.; B · HCl, m.p. 156°; chloroplatinate, m.p. 222°		105,106,166
4-Chloro-3,5-dinitropyridine	m.p. 240°		152
2,5-Dichloro-3-nitropyridine	m.p. 43°		5
2-Chloro-3,5-dinitropyridine	m.p. 102–3°	yellow prisms	191
2-Fluoro-5-nitropyridine	m.p. 19–21°; b.p. 79–81°		64
2-Iodo-5-nitropyridine	m.p. 165–66°		23
2,3-Dibromo-5-nitropyridine	m.p. 75–76°		17
6-Bromo-5-nitro-2-picoline	m.p. 71–72°		17
6-Bromo-3-nitro-2-picoline	m.p. 69–70°		17
3,6-Dibromo-5-nitro-2-picoline	m.p. 87–88°		17
5,6-Dibromo-3-nitro-2-picoline	m.p. 111–12.5°		17
6-Chloro-3-nitro-2-picoline	m.p. 67–69°; m.p. 53–55°	pale yellow needles	2,177,188
6-Chloro-4-nitro-2-picoline	1-oxide, m.p. 106–7°		15a

(*continued*)

TABLE VIII-6. Nitropyridines (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
6-Chloro-5-nitro-2-picoline	m.p. 52.5–54.5°		2
4-Chloro-3-nitro-2-picoline	m.p. 45–48°	needles	179
4-Chloro-5-nitro-2-picoline	m.p. 45–47°	needles	179
2-Chloro-4-nitro-3-picoline	1-oxide, m.p. 145–46°		15a
2-Chloro-5-nitro-3-picoline	m.p. 47–48°; b.p. 145.5°/18 mm.		71
6-Chloro-4-nitro-3-picoline	1-oxide, m.p. 154–55°		15a
6-Chloro-5-nitro-3-picoline	m.p. 50–51°	white crystals, sublimes *in vacuo*	45
2-Chloro-5-nitro-4-picoline	m.p. 38.5–39.5°; b.p. 91.2°/5 mm.		168
2-Chloro-3-nitro-4-picoline	m.p. 46–47°; m.p. 52–52.9°		17,168

TABLE VIII-7. Relative Reactivity of 2- and 4-Nitropyridines



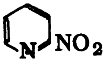
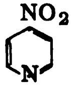
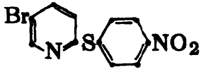
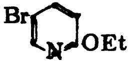
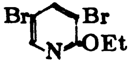
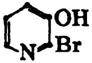
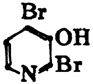
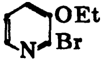
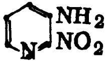
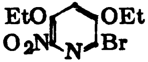
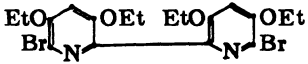
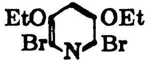
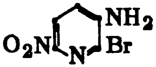
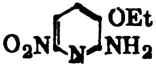
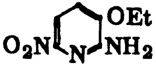
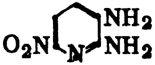
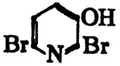
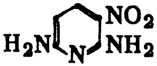
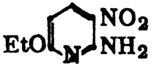
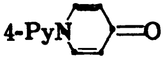
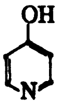
R	Product with 	Product with 
C_2H_5ONa	2-PyOEt	4-PyOEt
C_6H_5ONa	no reaction	4-PyOPh
28% NH_4OH (150°)	no reaction	4-PyOH
Aq. 10% KOH (100°)	2-PyOH	no reaction
Aq. 50% KOH (100°)		4-PyOH
$POCl_3$	no reaction	
Ac_2O	no reaction	4-PyOH

TABLE VIII-8. Replacement Reactions of 2- and 4-Nitropyridines

Compound	Reagent	Product (yield)	Ref.
5-Bromo-2-nitropyridine	p-$NO_2C_6H_4SNa$, 80°	 (37%)	1
5-Bromo-2-nitropyridine	NaOEt, 150°	 (50–55%)	79
3,5-Dibromo-2-nitropyridine	NaOEt, 100°		79
3-Ethoxy-2-nitropyridine	40% HBr-AcOH, 130°	 (80–85%)	79
3-Ethoxy-2-nitropyridine	40% HBr-AcOH, 130°	 (45%)	85
3-Ethoxy-2-nitropyridine	30–35% HBr-AcOH, 125°		85
3-Ethoxy-2-nitropyridine	NH_4OH, 140–150°	 (65–70%)	78
3,5-Diethoxy-2,6-dinitropyridine	30% HBr-AcOH, 100°	 (80%)	81,108
2-Bromo-3,5-diethoxy-6-nitropyridine	Br_2, $FeBr_2$, sunlight, 0°		82
2-Bromo-3,5-diethoxy-6-nitropyridine	Br_2, sunlight, 0°		82

2-Bromo-3-ethoxy-6-nitropyridine	NH_4OH, 140–150°		(70%)	78
			(9%)	
2-Bromo-3-ethoxy-6-nitropyridine	NH_4OH-EtOH, 190–200°		(40%)	78
			(3%)	
2-Bromo-3-ethoxy-6-nitropyridine	40% HBr-AcOH, 130°			85
2-Bromo-6-ethoxy-3-nitropyridine	NH_4OH, 85°		(90–100%)	78
2-Bromo-6-ethoxy-3-nitropyridine	NH_4OH-EtOH, 95°		(95%)	78
4-Nitropyridine	heat, 60°		(80–90%)	73
			(10%)	

(*continued*)

TABLE VIII-8. Replacement Reactions of 2- and 4-Nitropyridines (*continued*)

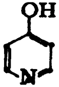
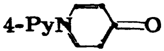
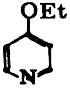
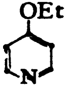
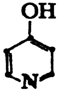
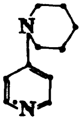
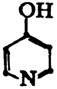
Compound	Reagent	Product (yield)	Ref.
4-Nitropyridine	H_2O, 60°	 (80–90%) +  (10%)	73
4-Nitropyridine	NaOEt-EtOH		96
4-Nitropyridine	C_6H_5ONa-C_6H_5OH		96
4-Nitropyridine	28% NH_4OH, 150–155°		96
4-Nitropyridine	50% KOH, 100°	same	96
4-Nitropyridine	piperidine		96
4-Nitropyridine	Ac_2O	 (+ NO)	96

TABLE VIII-9. Activation Energies of Nitrohalo Compounds in Halogen Replacement (8)

Compound	Reactants						
	Aniline	*p*-Toluidine	*p*-Anisidine	*m*-Toluidine	Pyridine	3-Picoline	4-Picoline
2-Chloro-5-nitropyridine	13,100	12,700	11,500	12,900	18,100	17,900	17,500
2-Chloro-3-nitropyridine	14,500	13,900		14,400	18,700	18,500	17,400
4-Chloro-3-nitropyridine					16,900	15,600	15,100
1-Chloro-2,4-dinitrobenzene	11,200	10,100	9,700		16,700	17,100	16,900

TABLE VIII-10. Reduction of 4-Nitropyridine 1-Oxide

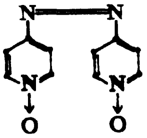
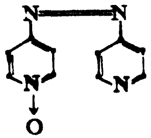
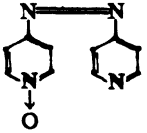
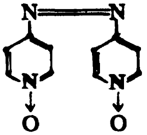
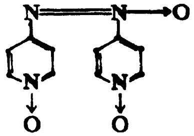
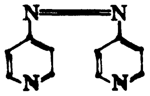
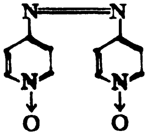
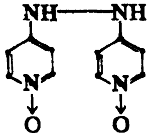
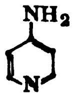
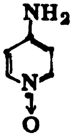
Reduction conditions	Product (yield)	Ref.
As$_2$O$_3$, NaOH, reflux 2 hrs.	 (65%) +  (trace)	77
Na$_2$SnO$_2$, reflux 2 hrs.	 (65%)	77
NaNO$_2$-NaOH, 50° or NH$_4$OH-H$_2$S, 15°		132
Zn-H$_2$O, 100° or Zn-AcOH, 25°		132
15% NaOH, reflux 3 hrs.	 (34%)	74
NH$_3$-C$_2$H$_5$OH or C$_6$H$_5$CH$_2$NH$_2$		142
SnCl$_2$-HCl, 100°		132
H$_2$S-NH$_4$OH, 100°		132
H$_2$-Pd(EtOH)		132

TABLE VIII-10 (*continued*)

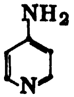
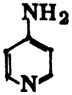
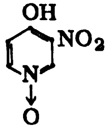
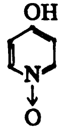
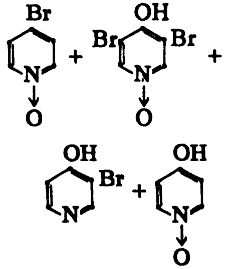
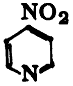
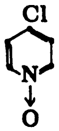
Reduction conditions	Product (yield)	Ref.
(1) $Na_2S_2O_4$; (2) HCl		132
H_2-Pd (HCl)		132

TABLE VIII-11. Reactions of 4-Nitropyridine 1-Oxides

Compound	Reagent	Product (yield)	Ref.
4-Nitropyridine 1-oxide	Ac_2O, air, 100°	 (38%)	72,132
	Ac_2O, air, dimethylaniline, 100°		72,132
	48% HBr, urea, 160°		139
	KNO_3, H_2SO_4, 165°		95
	25% HCl, 160°	 (70–80%)	74

(*continued*)

TABLE VIII-11. Reactions of 4-Nitropyridine 1-Oxides (*continued*)

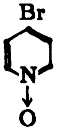
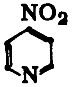
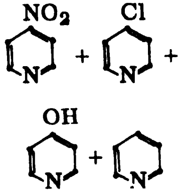
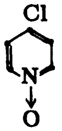
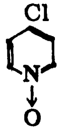
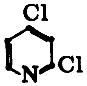
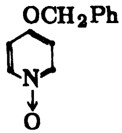
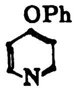
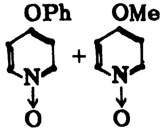
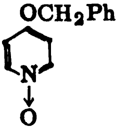
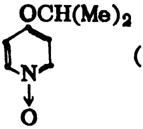
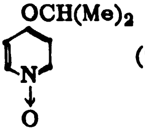
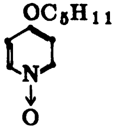
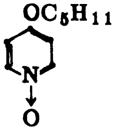
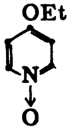
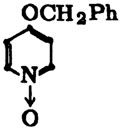
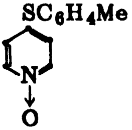
Compound	Reagent	Product (yield)	Ref.
4-Nitropyridine 1-oxide (*cont.*)	30% HBr-AcOH, 120°	 (70–80%)	74
	PCl_3-$CHCl_3$, 70–80°	 (79%)	68,69, 132
	PCl, 70–80° (SO_2Cl_2, $SOCl_2$, CH_3COCl also reported to give similar results.)		69
	CH_3COCl, 50°	 (92%)	75,92, 132
	$POCl_3$, 100°	 (57%)	138
	SO_2Cl_2, 110°	 (35–40%)	115
	$NaOCH_2Ph$		147
	NaOPh-PhOH		142
	PhOH-MeOH	 (2:1)	98

TABLE VIII-11 (*continued*)

Compound	Reagent	Product (yield)	Ref.
4-Nitropyridine 1-oxide (*cont.*)	PhCH$_2$OH-MeOH		98
	(Me)$_2$CHOH, MeOH	 (64%)	98
	(Me)$_2$CHOH-dimethyl-aniline	 (91%)	98
	C$_5$H$_{11}$OH-MeOH	 (23%)	98
	C$_5$H$_{11}$OH-dimethyl-aniline	 (26%)	98
	NaOH-EtOH	 (65–70%)	74
	NaOCH$_2$Ph, 25°	 (80%)	132
	p-MeC$_6$H$_4$SNa	 (65%)	138

(*continued*)

TABLE VIII-11. Reactions of 4-Nitropyridine 1-Oxides (*continued*)

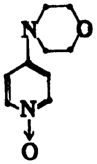
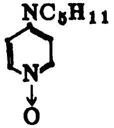
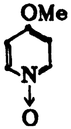
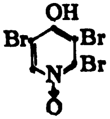
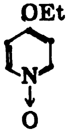
Compound	Reagent	Product (yield)	Ref.
4-Nitropyridine 1-oxide (*cont.*)	morpholine	 (low)	91,138
	piperidine	 (low)	91
	NH_2OH-MeOH (KOH)		142
1-Bromo-4-nitropyridine 1-oxide	H_2O_2, aq. NaOH	 (good)	75
4-Nitro-2-picoline 1-oxide	NaOEt-EtOH		90,142

TABLE VIII-12. Nitroso- and Hydroxylaminopyridines

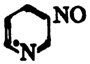
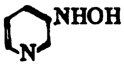
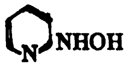
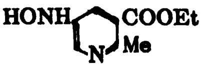
Compound	M.p., °C.	Remarks	Ref.
	94	colorless crystals; sublimes; yields a green melt and forms green solutions	104
	109	colorless needles; reduces Fehling's solution and ammoniacal $AgNO_3$; readily oxidizes in air	104
	83–85	sublimes *in vacuo*; color reaction with $FeCl_3$; unstable	131
	111.5–12.5		55

TABLE VIII-13. Preparation of Azopyridines by Oxidation of Aminopyridines

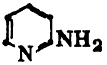
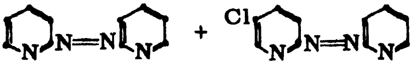
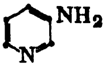
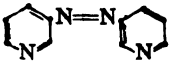
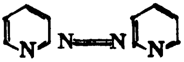
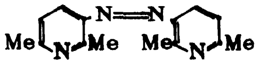
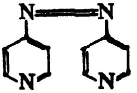
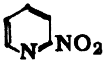
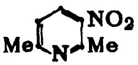
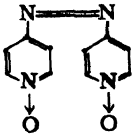
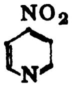
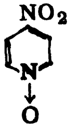
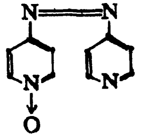
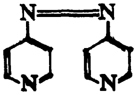
Aminopyridine	Oxidizing agent	Product	Ref.
	NaOCl		102
	[NaOI]		173

TABLE VIII-14. Reduction of Nitropyridines to Azo Derivatives

Nitropyridine	Reduction conditions	Product	Ref.
	As_2O_3, NaOH		102
	Na_2SnO_2		140
	Na_2SnO_2		74
	$NaNO_2$, NaOH, 50°		141
	or H_2S-NH_4OH, EtOH, 15°		141
	or NH_3-EtOH, heat		142
	or $PhCH_2NH_2$-EtOH, heat		142
	or electrolytic		146
	or As_2O_3, NaOH, reflux		77
	Na_2SnO_2, reflux		77
	aq. NaOH	 (low yield)	74

(continued)

TABLE VIII-14. Reduction of Nitropyridines to Azo Derivatives (*continued*)

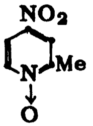
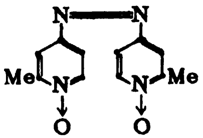
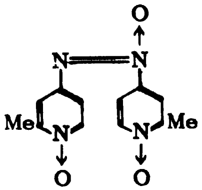
Nitropyridine	Reduction conditions	Product	Ref.
	H_2S-NH_4OH, EtOH or NaOH-$NaNO_2$, 45°		143 143
	$SnCl_2$, HCl	above + 	143

TABLE VIII-15. Preparation of Azopyridines from Hydrazopyridines

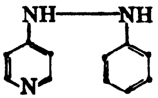
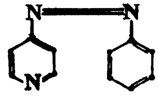
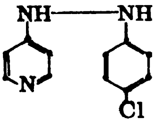
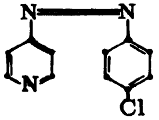
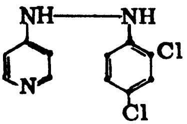
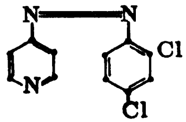
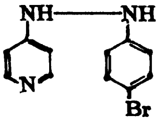
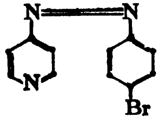
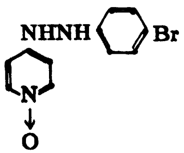
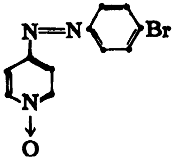
Hydrazopyridines	Oxidizing agent	Product	Ref.
	HNO_2		107
	air, 50% NaOH		107
	2*N* NaOH, reflux		107
	air, 50% NaOH		107
	benzene, heat, or AcOH, heat		46a

TABLE VIII-15 (*continued*)

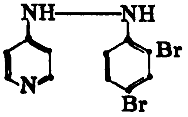
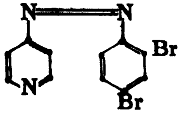
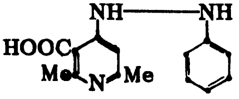
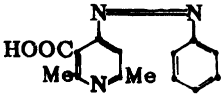
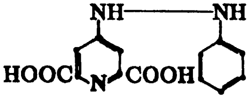
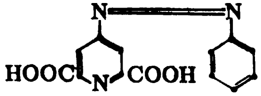
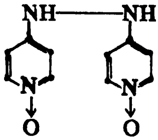
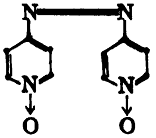
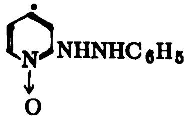
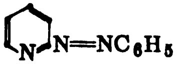
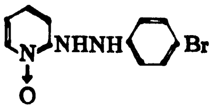
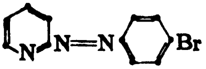
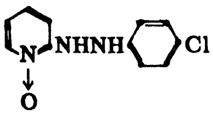
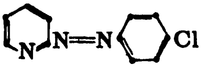
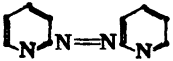
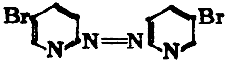
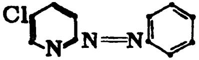
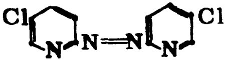
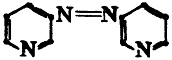
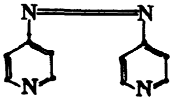
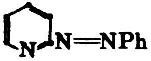
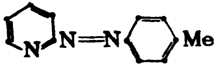
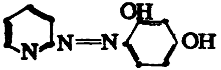
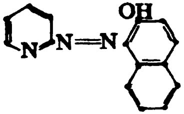
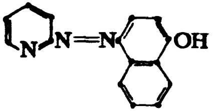
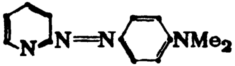
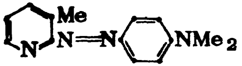
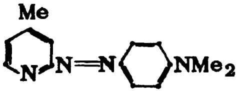
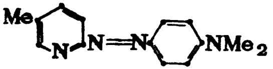
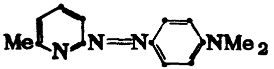
Hydrazopyridines	Oxidizing agent	Product	Ref.
	reflux, 10% NaOH		107
	dil. HNO$_3$	 35%	107
	air		39
			132
	EtOAc or AcOH, heat		46a
	benzene, heat, or AcOH, heat		46a
	benzene, heat, or AcOH, heat		46a

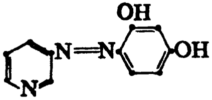
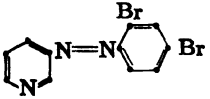
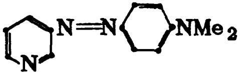
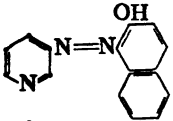
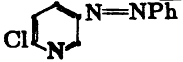
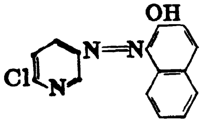
TABLE VIII-16. Properties of Azopyridines

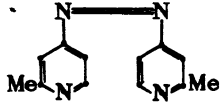
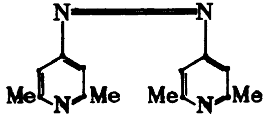
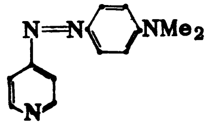
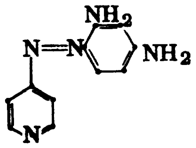
Compound	Physical properties, derivatives	Remarks	Ref.
	*trans*, m.p. 83°, 87°; *cis*, 87°; nitrate, m.p. 158° (dec.); picrate, m.p. 180°(dec.)	orange-red; *cis*, deep red needles; *cis-trans* eutectic, m.p. 56	21,100,102, 103,118
	m.p. 240–41°		19
	m.p. 135°		100
	m.p. 248° (dec.)		18,100
	*cis*, m.p. 82°; *trans*, m.p. 140°, 141°, 142°, 138–39°		19,58,83,22
	m.p. 107.5–8; 1-oxide, m.p. 160–61°; 1,1′-dioxide, m.p. 253–54°, 243°		77,132,141
	m.p. 50–52°; picrate, m.p. 135–37°; 141°; methiodide, m.p. 162–63°; 1-oxide, m.p. 111–12°		46a,48,54
	m.p. 72–74°	red needles	54
2-(*p*-Bromophenylazo)pyridine	m.p. 122–23°; 1-oxide, m.p. 206–7°		46a,48
2-(2,4-Dibromophenylazo)-pyridine	m.p. 151–52°; 1-oxide, m.p. 200–1°		48

2-(*p*-Chlorophenylazo)pyridine	m.p. 115–18°, 120°, 123–24°; 1-oxide, m.p. 200–1°		46a,48,54
2-(2,4-Dichlorophenylazo)pyridine	m.p. 147–48°		48
	m.p. 186–88° (dec.)	orange crystals	54
	m.p. 137°	orange-red needles	27,42
		red dyestuff; two isomers with different colors in H_2SO_4	27,42
	*cis*, m.p. 108–9°; *trans*, m.p. 111–12°	*cis*, orange plates; *trans*, red plates	54
	m.p. 158–60°		54
	m.p. 151–53°		54
	m.p. 154–57°		54
	m.p. 107–8°		54

(*continued*)

TABLE VIII-16. Properties of Azopyridines (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
6-Chloro-2-phenylazopyridine	m.p. 114°		48
6-Chloro-2-(*p*-chlorophenylazo)pyridine	1-oxide, m.p. 175°		48
	m.p. 218° (dec.)	brown prisms	129,164
	m.p. 133–35°		48
	m.p. 121°; hydrochloride, m.p. 105° (dec.)	yellow-red	164
	m.p. 152°; hydrochloride, m.p. 160° dec.		164
	m.p. 108–9°	orange prisms	128
	m.p. 185°		155

	m.p. 224-25°; 1,1'-dioxide, m.p. 224-25, red needles	red needles	117a,132, 140,143
	m.p. 137-38°		140
4-Phenylazopyridine	m.p. 98-99°; hydrochloride, m.p. 175-80° (dec); methiodide, m.p. 188°; 1-oxide, m.p. 149-50°		48,70,98,107
4-(*p*-Bromophenylazo)-pyridine	1-oxide, m.p. 206-7°		48
4-(*p*-Chlorophenylazo)-pyridine	m.p. 99-100°; 1-oxide, m.p. 185°		48,107
4-(2,4-Dibromophenyl-azo)pyridine	1-oxide, m.p. 199-200°		48
4-(2,4-Dichlorophenyl-azo)pyridine	m.p. 110-11; 1-oxide, m.p. 209-10°		48,107
	m.p. 207-9°; dinitrate, m.p. 76-77°		107,111
	m.p. 263-64°		111

(*continued*)

TABLE VIII-16. Properties of Azopyridine (*continued*)

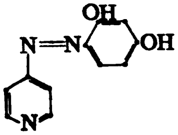
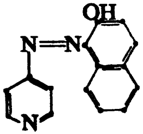
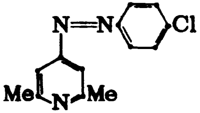
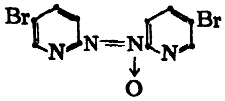
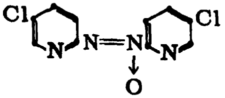
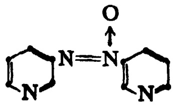
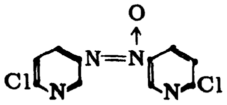
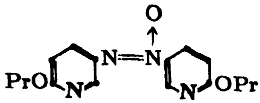
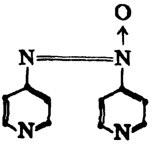
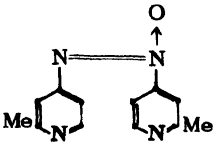
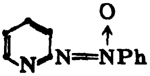
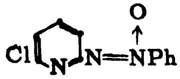
Compound	Physical properties, derivatives	Remarks	Ref.
		dark red; yellow in acid, red-brown in alkali	111
	m.p. 228–29° (dec.)	red needles	140
	m.p. 99–100°	orange needles	107

TABLE VIII-17. Azoxypyridines

Compound	Physical properties, derivatives	Remarks	Ref.
	dec. 200°		18
	dec. 204°		18
	m.p. 130–31°, 125–26°, 128–29	lustrous crystals; gives yellow melt	22,58, 99
	m.p. 188°		7
	m.p. 97–98°		7
	m.p. 125–26°; 1-oxide, m.p. 160–61°; 1,1′-dioxide, m.p. 223–24°, 236–37°	orange-yellow needles	77,132
	m.p. 220–21° (dec.)	orange-yellow needles	132
	1,1′-dioxide, m.p. 234–35° (dec.)		117a
	1-oxide, m.p. 138°		48
	m.p. 108–9°		48

(continued)

TABLE VIII-17. Azoxypridines (*continued*)

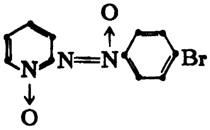
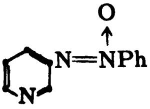
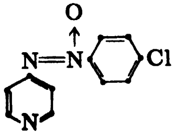
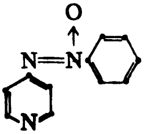
Compound	Physical properties, derivatives	Remarks	Ref.
			
	1-oxide, m.p. 89–90°		48
	1-oxide, m.p. 174–76°		48
			48

TABLE VIII-18. Hydrazinopyridines

Compound	Physical properties, derivatives	Remarks	Ref.
2-Hydrazinopyridine	b.p. 185°/140 mm.; 170°/55 mm.; 145°/25 mm.; 140°/20 mm.; m.p. 46°; picrate, m.p. 160–61° (dec.); chloroplatinate, m.p. 256° (dec.)	white solid, dec. rapidly on exposure to air	41,56
2-(*N,N*-Dimethylhydrazino)pyridine	m.p. 95°; picrate, m.p. 185°; dihydrochloride, m.p. 134°		98a
3-Hydrazinopyridine	m.p. 53–55°; benzal der., m.p. 163–65°	dec. on exposure to air	34,164,218
4-Hydrazinopyridine	b.p. 185–87°/18 mm.; hydrochloride, m.p. 238°; 1-oxide, m.p. 183–85 (dec.); 1-oxide picrate, m.p. 192–93° (dec.)	colorless oil, very unstable	112,113 98b
2-Hydrazino-5-iodopyridine			237
2-Hydrazino-5-nitropyridine	m.p. 203–4° (dec.); benzal der., m.p. 226–28°		46,210,218, 221
2-Hydrazino-6-nitro-3-pyridinol	m.p. 180–82°; isopropylidene der., m.p. 170–72°		50a
2-Hydrazino-3,5-dinitropyridine	m.p. 173°	greenish black iridescent crystals	158
6-Hydrazino-5-nitro-3-picoline	m.p. 167–68°		15
2-Chloro-5-hydrazinopyridine	m.p. 129–30°	reduces Fehling's solution	207

(*continued*)

TABLE VIII-18. Hydrazinopyridines (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
3-Chloro-6-hydrazinopyridine	m.p. 135°		50a
4-Hydrazino-3-nitropyridine	m.p. 200°	yellow solution in acid, deep blue in alkali	105
4-Hydrazino-3,5-dinitropyridine	m.p. 161–61.5°; isopropylidene der., m.p. 170–71°		
Ethyl 6-chloro-4-hydrazinonicotinate	m.p. 147–48°		86
4-Hydrazino-2,6-pyridinedicarboxylic acid	sinters 295°; hydrochloride, m.p. 212°; (dec.); benzal der., m.p. 278–80° (dec.)	reduces Fehling's solution, ammoniacal $AgNO_3$	113
Ethyl 4-hydrazino-2,6-dimethylnicotinate		condenses readily	126
6-Chloro-4-hydrazino-2-hydroxynicotinonitrile	m.p. 150° (dec.)		174
N-Methyl-*N*-(2-pyridyl)hydrazine	b.p. 105°/10 mm.; picrate, m.p. 153–55°; benzal der., m.p. 67–68°		37
N-Methyl-*N*-(3-pyridyl)hydrazine	b.p. 191°/11 mm.		159

2-Phenylhydrazinopyridine	1-oxide, m.p. 136°	48
2-(*p*-Bromophenyl)hydrazinopyridine	m.p. 110–12; 1-oxide, m.p. 139°; hydrobromide, m.p. 220°	48
2-(*p*-Chlorophenyl)hydrazinopyridine	m.p. 110–12°; 1-oxide, m.p. 132° (dec.); hydrochloride, m.p. 226°	48
2-(2,4-Dichlorophenyl)hydrazinopyridine	m.p. 113–15°; hydrochloride, m.p. 219–20°	48
6-Chloro-2-phenylhydrazinopyridine	m.p. 126–28°	48
3-Phenylhydrazinopyridine	m.p. 134–35°	48
4-(*p*-Bromophenyl)hydrazinopyridine	hydrobromide, m.p. 173–76°	48
4-(2,4-Dibromophenyl)hydrazinopyridine	1-oxide, m.p. 177–78°	48
4-(*p*-Chlorophenyl)hydrazinopyridine	1-oxide, m.p. 203–5°	48
4-(2,4-Dichlorophenyl)hydrazinopyridine	1-oxide, hydrochloride, m.p. 164–67°	48
2-(*N*-Benzyl-*N*-phenyl)hydrazinopyridine	m.p. 61–62°	47
2-(*N*,*N*-Diphenyl)hydrazinopyridine	m.p. 160–61°; hydrochloride, m.p. 189–91°	47
2,4,6-Tris(*N*,*N*-Dimethylhydrazino)pyridine	m.p. 154°; trihydrochloride, m.p. 214°	98a

TABLE VIII-19. Pyridotriazoles, Pyridotetrazoles, and Related Systems

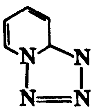
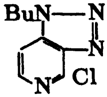
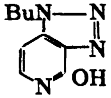
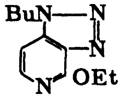
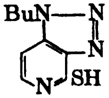
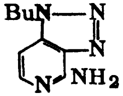
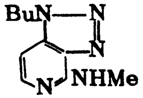
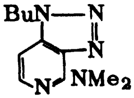
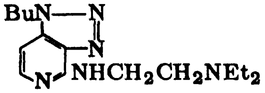
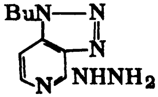
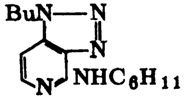
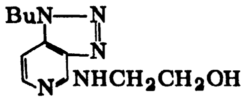
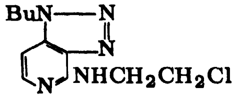
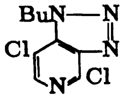
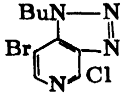
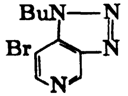
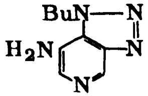
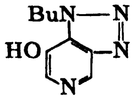
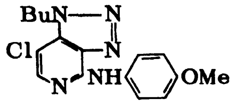
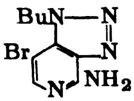
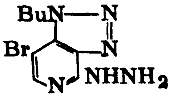
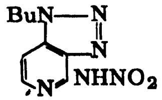
Compound	Preparative method	Physical properties, derivatives	Ref.
	from 2-PyNHNH$_2$ + HNO$_2$	m.p. 159°	10,56, 121
	from 3-amino-4-butylamino-2-chloropyridine + HNO$_2$	m.p. *ca.* 10°; b.p. 171–72°/3 mm.	14
	replacement of 2-halo function	m.p. 233°	14
	replacement of 2-halo function	m.p. 50–51°	14
	replacement of 2-halo function	m.p. 203–4°	14
	replacement of 2-halo function	m.p. 176–77°	14
	replacement of 2-halo function	m.p. 93–94°	14
	replacement of 2-halo function	b.p. 160–61°/3 mm.; picrate, m.p. 119–20°	14
	replacement of 2-halo function	b.p. 209–10°/3 mm.	14
	replacement of 2-halo function	m.p. 80°	14
	replacement of 2-halo function	m.p. 74°	14

TABLE VIII-19 (*continued*)

Compound	Preparative method	Physical properties, derivatives	Ref.
	replacement of 2-halo function	m.p. 78–79°; hydrochloride, m.p. 193–94°	14
	replacement of 2-halo function	hydrochloride, m.p. 190° (dec.)	14
	from 3-amino-4-butylamino-2,5-dichloropyridine + HNO_2	m.p. 48°; b.p. 198°/3 mm.	14
	from 3-amino-4-butylamino-5-bromo-2-chloropyridine + HNO_2	m.p. 66–67°	14
	from 3-amino-4-butylamino-5-bromopyridine + HNO_2	m.p. 43–44°; b.p. 151–53°/3 mm.; picrate, m.p. 122–23°	14
	by ammonolysis of bromo compound at 70–80°	m.p. 148°	14
	by diazotization of corres. amino compound	m.p. 109–10°	14
	replacement of 2-halo function	m.p. 103–4°	14
	replacement of 2-halo function	m.p. 222°	14
	replacement of 2-halo function	m.p. 124°	14
	nitration of amino compound to nitramine	m.p. 165–66° (dec.)	14

(*continued*)

TABLE VIII-19. Pyridotriazoles and Pyridotetrazoles (*continued*)

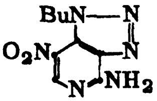
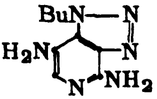
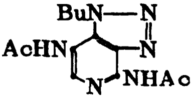
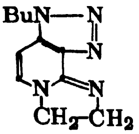
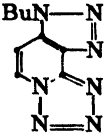
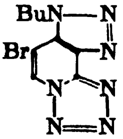
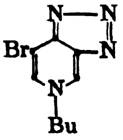
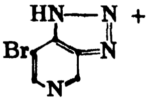
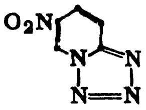
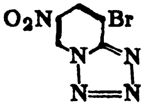
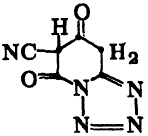
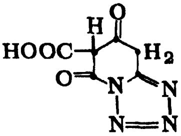
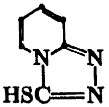
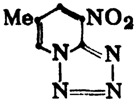
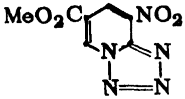
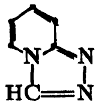
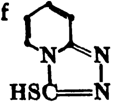
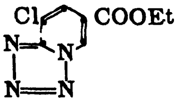
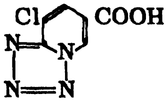
Compound	Preparative method	Physical properties, derivatives	Ref.
	nitration for prolonged period	m.p. 259°	14
	reduction of corres. nitro compound with SnCl$_2$	m.p. 202–3°; hydrochloride, m.p. 266–67° (dec.)	14
	acetylation of corres. amino compound	m.p. 205–6°	14
	from 2-(β-chloroethyl)amino compound by heating at 170°	m.p. 75°; ethiodide, m.p. 176°	14
	from corres. hydrazinopyridine + HNO$_2$	m.p. 157–58°	14
	from corres. hydrazinopyridine + HNO$_2$	m.p. 114°	14
	from  + BuI-KOH, 150–60°	m.p. 106°; b.p. 167–68°/3 mm.	14
	from corres. hydrazinopyridine + HNO$_2$	m.p. 142–43°	14
	from corres. hydrazinopyridine + HNO$_2$	m.p. 125°	14

TABLE VIII-19 (*continued*)

Compound	Preparative method	Physical properties, derivatives	Ref.
	from corres. hydrazinopyridine + HNO_2		175
	from nitrile by hydrolysis	m.p. 195° (dec.); Me ester, m.p. 198° (dec.)	175
	2-pyridylhydrazine, CS_2, reflux 20 hrs.; 2-pyridylhydrazine + $CSCl_2$; K_2CS_3, EtOH—AcOH, reflux 2 hrs.	m.p. 209–10° (205–6°)	127, 193, 200
	from 6-chloro-5-nitro-3-picoline + NaN_3	m.p. 151–51.5°	11
	from methyl 6-chloro-5-nitronicotinate + NaN_3	m.p. 117°; free acid m.p. 189.5–90° (dec.)	11
	from 2-pyridylhydrazine + anhyd. HCO_2H, heat; from dil. HNO_3 oxidation of 	chloroplatinate does not melt at 300°	56
	from corres. hydrazinopyridine + HNO_2		62
	from corres. hydrazinopyridine + HNO_2	m.p. 195–96°	62

(*continued*)

TABLE VIII-19. Pyridotriazoles and Pyridotetrazoles (*continued*)

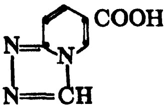
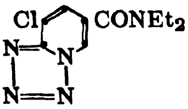
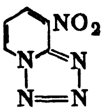
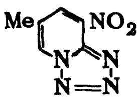
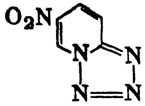
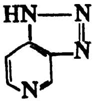
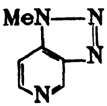
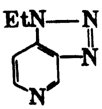
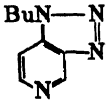
Compound	Preparative method	Physical properties derivatives	Ref.
	from 2-pyridylhydrazine + anhyd. HCO_2H, heat		62
	from 2-pyridylhydrazine + anhyd. HCO_2H, heat	m.p. 115–16°	62
	from 2-chloro-3-nitropyridine + NaN_3	m.p. 167–68°	10,11
	from corres. halopyridine + NaN_3	m.p. 151–51.5°	11
	from 2-chloro-5-nitropyridine + NaN_3	m.p. 138–40°	10
	from 3,4-diaminopyridine + HNO_2	m.p. 240°; hydrochloride m.p. 210° (dec.)	12
	from 3-amino-4-methylaminopyridine + HNO_2	m.p. 120°; picrate, m.p. 178.5°; hydrochloride, m.p. 233° (dec.); ethiodide, m.p. 194–95°	12
	from 3-amino-4-ethylaminopyridine + HNO_2	m.p. 48°; b.p. 121.5°/1 mm.; picrate, m.p. 177°; hydrochloride, m.p. 183°; ethiodide, m.p. 166–67°	12
	from 3-amino-4-butylaminopyridine + HNO_2	b.p. 128°/1 mm.; hydrochloride, m.p. 148°	12

TABLE VIII-19 (*continued*)

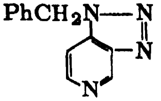
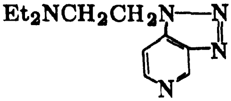
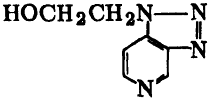
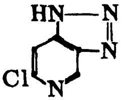
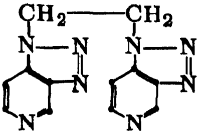
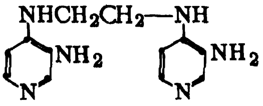
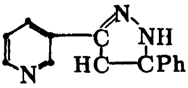
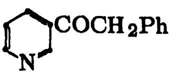
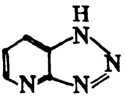
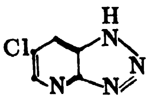
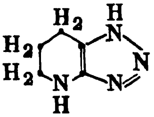
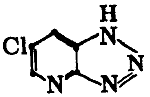
Compound	Preparative method	Physical properties, derivatives	Ref.
	from 3-amino-4-benzylamino-pyridine + HNO_2	m.p. 124°; hydrochloride, m.p. 148°	
	from 3-amino-4-(diethylamino-ethyl)amino-pyridine + HNO_2	b.p. 147°/1 mm.	12
	from 3-amino-4-(hydroxyethyl)-aminopyridine + HNO_2	m.p. 143-44°	12
	from 3,4-diamino-6-chloropyridine + HNO_2	m.p. 157-58°	12
	from  + HNO_2	m.p. 270° (dec.)	12
	from  + N_2H_4	m.p. 187-88°	130
	by diazotization of corres. amino compound	m.p. 206-7°	197
	by diazotization of corres. amino compound	m.p. 166-67°	197
	by catalytic reduction of 	m.p. 164-65°	197

TABLE VIII-20. Side-Chain Derivatives

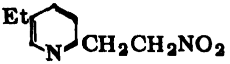
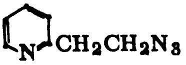
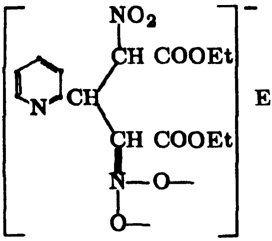
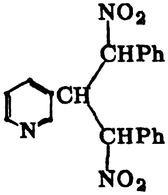
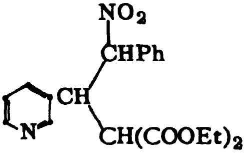
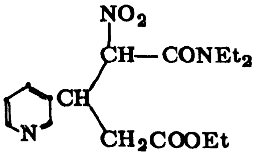
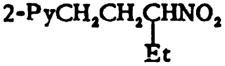
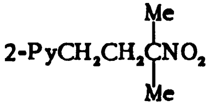
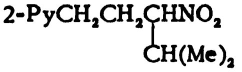
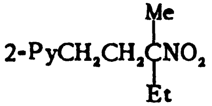
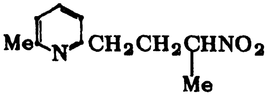
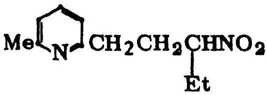
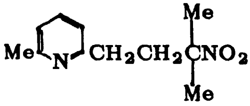
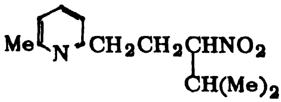
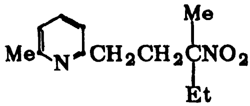
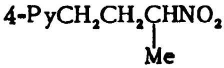
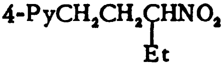
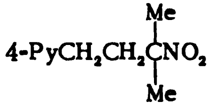
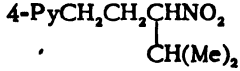
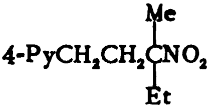
Compound	Physical properties, derivatives	Remarks	Ref.
2-$PyCH_2CH_2NO_2$	m.p. 145		214
4-$PyCH_2CH_2NO_2$			214
			214
	b.p. 65°/1 mm.; vig. dec. with H_2SO_4, 60°; picrate, m.p. 112-13°		9
2-$PyCH{:}CHNO_2$	m.p. 141°		51
 $Et_2NH_2^+$	m.p. 140.5°		52
	m.p. 129°		51
	m.p. 120.5°		51
	m.p. 117°		51
4-$PyCH_2NHNH_2$	dihydrochloride, m.p. 167°		
2-$PyCH_2CH_2\underset{Me}{CH}NO_2$	b.p. 116-17°/0.4 mm.; $n_D^{20} = 1.5187$	light yellow oil	163a
 2-$PyCH_2CH_2\underset{Et}{CH}NO_2$	b.p. 133-36°/0.8 mm.; $n_D^{20} = 1.5136$	orange-yellow oil	163a

TABLE VIII-20 (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
 $2\text{-PyCH}_2\text{CH}_2\overset{\text{Me}}{\underset{\text{Me}}{\text{C}}}\text{NO}_2$	b.p. 117-19°/1.5 mm.; n_D^{20} = 1.5179		163a
 $2\text{-PyCH}_2\text{CH}_2\underset{\text{CH(Me)}_2}{\text{C}}\text{HNO}_2$	b.p. 143-46°/0.6 mm.; n_D^{20} = 1.5106	yellow oil	163a
 $2\text{-PyCH}_2\text{CH}_2\overset{\text{Me}}{\underset{\text{Et}}{\text{C}}}\text{NO}_2$	b.p. 131-33°/1.4 mm.; n_D^{20} = 1.5181		163a
	b.p. 103-7°/0.8 mm.; n_D^{20} = 1.5158	yellow oil	163a
	b.p. 111-13°/0.6 mm.; n_D^{20} = 1.5090	orange oil	163a
	b.p. 109-11°/0.5 mm. n_D^{20} = 1.5122	greenish oil	163a
	b.p. 126-29°/0.9 mm.; n_D^{20} = 1.5090	greenish oil	163a
	b.p. 108-14°/0.8 mm.; n_D^{20} = 1.5081	greenish oil	163a
 $4\text{-PyCH}_2\text{CH}_2\underset{\text{Me}}{\text{C}}\text{HNO}_2$	b.p. 124-27°/0.6 mm.; n_D^{20} = 1.5176	yellow oil	163a
 $4\text{-PyCH}_2\text{CH}_2\underset{\text{Et}}{\text{C}}\text{HNO}_2$	b.p. 124-28°/0.4 mm. n_D^{20} = 1.5131	light orange oil	163a
 $4\text{-PyCH}_2\text{CH}_2\overset{\text{Me}}{\underset{\text{Me}}{\text{C}}}\text{NO}_2$	b.p. 130-31°/0.7 mm.; n_D^{20} = 1.5135	greenish oil	163a
 $4\text{-PyCH}_2\text{CH}_2\underset{\text{CH(Me)}_2}{\text{C}}\text{HNO}_2$	b.p. 142-45°/0.5 mm.; n_D^{20} = 1.5120	yellow oil	163a

(*continued*)

TABLE VIII-20. Side-Chain Derivatives (*continued*)

Compound	Physical properties, derivatives	Remarks	Ref.
 $4\text{-}PyCH_2CH_2\overset{Me}{\underset{Et}{C}}NO_2$	b.p. 117-19°/0.4 mm.; $n_D^{20} = 1.5130$	yellow oil	163a

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